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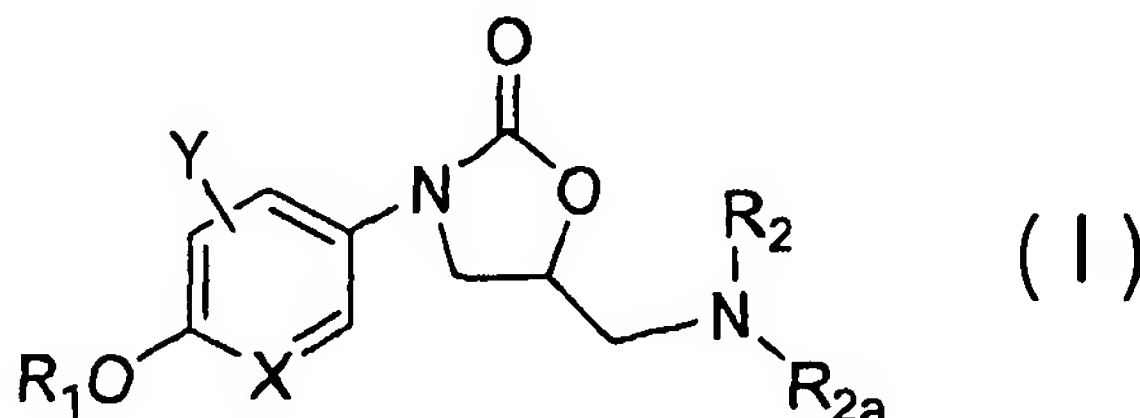
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(54) Title: **PIPERIDINYLOXY AND PYRROLIDINYLOXYPHENYL OXAZOLIDINONES AS ANTIBACTERIALS**



(57) Abstract: Piperidinyloxy, pyrrolidinyloxy and azetidinyloxy compounds of the formula (I): wherein R₁ is a piperidinyloxy, pyrrolidinyloxy or azetidinyloxy moiety as described herein and in which the substituents have the meaning indicated in the description. These compounds are useful as antibacterial agents.

PIPERIDINYLOXY AND PYRROLIDINYLOXYPHENYL OXAZOLIDINONES AS ANTIBACTERIALS

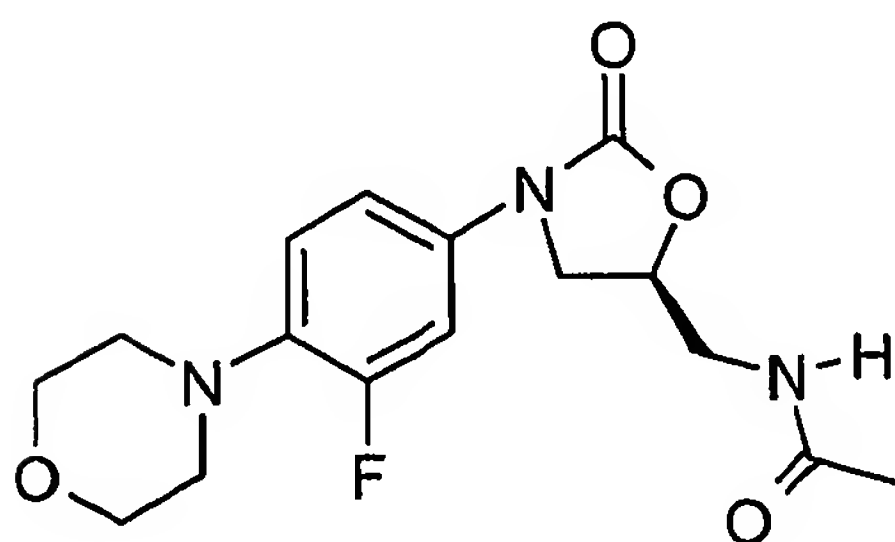
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FIELD OF THE INVENTION

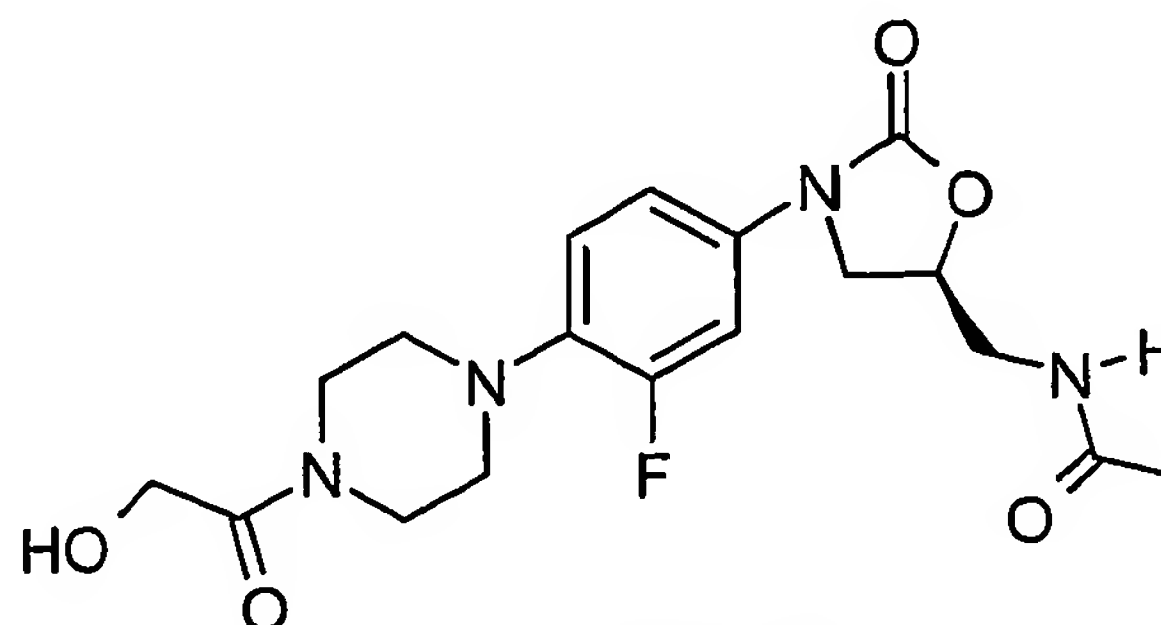
The present invention relates to the field of piperidinyloxy, pyrrolidinyloxy and azetidinyloxy oxazolidinone compounds having antibacterial activity,
10 pharmaceutical compositions containing the compounds, and methods of treating bacterial infections with the compounds.

BACKGROUND OF THE INVENTION

15 Oxazolidinones have been identified, within the last twenty years, as a new class of antibacterials which are active against numerous multidrug-resistant gram positive organisms. Particularly problematic pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. As
20 a class oxazolidinones exhibit a unique mechanism of action. Studies have shown that these compounds selectively bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of protein synthesis. Exemplary members of oxazolidinones are linezolid (see WO 95/07271) and eperezolid.



linezolid



eperezolid

25

The following references relate to various oxazolidinone type compounds disclosed as having antibacterial activity:

U.S. Pat. No. 4,705,799 to W. A. Gregory discloses aminomethyl
5 oxooxazolidinyl benzene derivatives, including the sulfides, sulfoxides, sulfones and sulfonamides, such as (1)-N-[3-[4-(methylsulfinyl)-phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

U.S. Pat. No. 5,565,571 to Barbachyn et al. discloses substituted aryl- and heteroarylphenyloxazolidinones.

10 U.S. Pat. No. 5,792,765 to Riedl et al. relates to new substituted oxazolidinones.

U.S. Pat. No. 5,910,504 to Hutchinson discloses phenyloxazolidinone compounds having a nitrogen containing hetero-aromatic ring substitution attached through one of the nitrogen atoms.

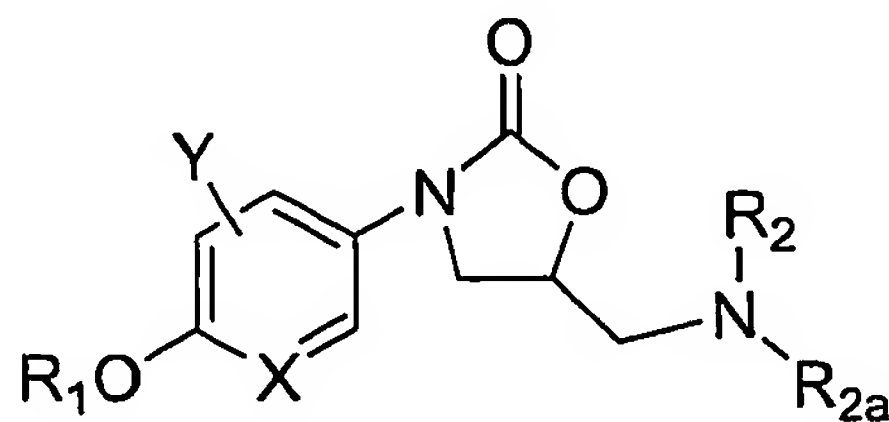
15 WO 93/09103 (Barbachyn et al.) discloses substituted aryl- and heteroarylphenyloxazolidinones.

WO 95/07271 (Barbachyn et al.) discloses oxazine and thiazine oxazolidinone derivatives.

20 WO 98/54161 (Hester et al.) provides oxazolidinone antibacterial agents having a thiocarbonyl functionality.

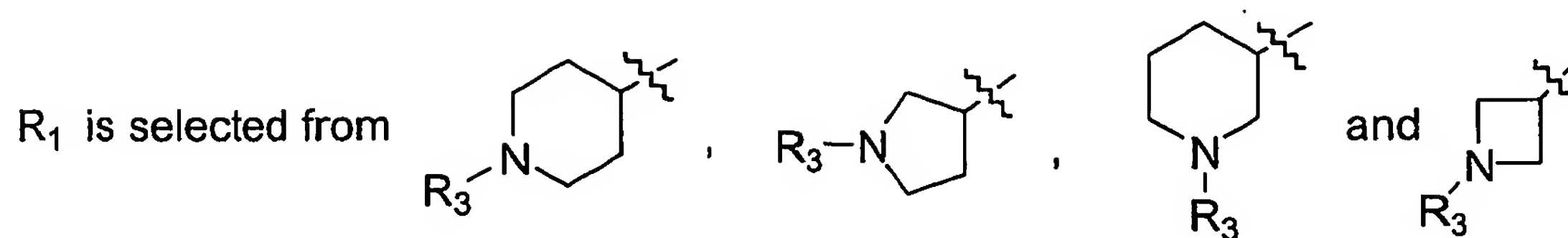
SUMMARY OF THE INVENTION

25 The invention provides new piperidinyloxy, pyrrolidinyloxy and azetidinyloxy compounds of Formula I



Formula I

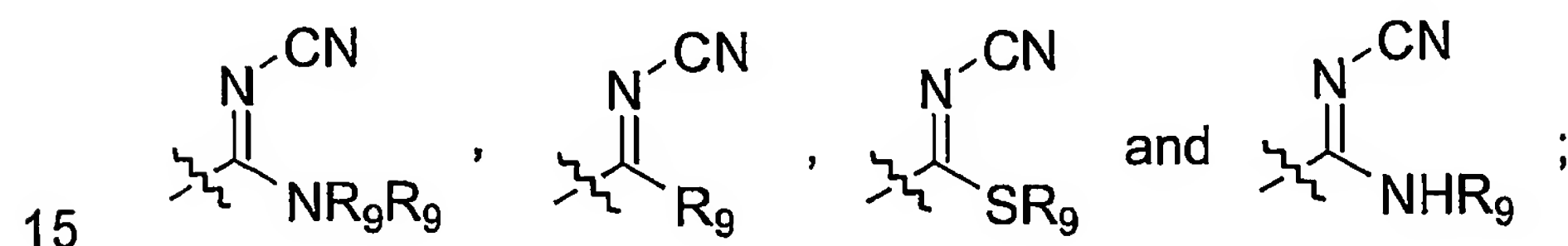
30 wherein



wherein

- (a) R_3 is selected from H, alkyl, $-\text{COR}_4$, $-(\text{CH}_2)_t\text{heteroaryl}$, $-\text{CHR}_5\text{R}_6$, $-(\text{CH}_2)_t\text{aryl}$, $-\text{SO}_2\text{NR}_5\text{R}_8$, and $-\text{SO}_2\text{R}_9$;
- 5 (b) R_4 is selected from H, $-\text{OR}_5$, alkyl, alkylaryl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, $-(\text{CH}_2)_t\text{OR}_5$, $-(\text{CH}_2)_t\text{NR}_7\text{R}_8$, $-\text{CHR}_5\text{R}_6$, and $-\text{NR}_5\text{R}_6$ optionally forming a cyclic amino derivative;
- (c) R_5 and R_6 are independently selected from H, alkyl, alkylaryl, haloaryl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, and acyl;
- 10 (d) R_7 and R_8 are independently selected from H, alkyl, $-\text{COR}_9$, $-\text{SO}_2\text{R}_9$ and $-\text{CO}_2\text{R}_9$; and
- (e) R_9 is selected from H, alkyl, aryl and alkylaryl;

R_2 is selected from $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$,



R_{2a} is H or acyl with the proviso that when R_3 is selected from alkyl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, and $-\text{CHR}_5\text{R}_6$, R_{2a} is H;

20 X is N or CH;

Y is selected from H, halogen, alkoxy, and alkyl; and

t is an integer of 0 to 4;

25

or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, or a pharmaceutically acceptable salt thereof.

30 Compounds of the above formula are useful as antibacterial agents for the treatment of bacterial infections in a subject such as human and animal.

The present invention is also directed to a method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said subject a therapeutically effective amount of the compound of Formula I.

5

The present invention is further directed to a method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective amount of the compound of Formula I.

10

Other objects and advantages will become apparent to those skilled in the art from a review of the ensuing specification.

15

DETAILED DESCRIPTION

Relative to the above description, certain definitions apply as follows.

Unless otherwise noted, under standard nomenclature used throughout this disclosure the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment.

20

Unless specified otherwise, the terms "alkyl", "alkenyl", and "alkynyl," whether used alone or as part of a substituent group, include straight and branched chains having 1 to 8 carbon atoms, or any number within this range. For example, alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl and 2-methylpentyl. "Alkoxy" radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. "Cycloalkyl" groups contain 3 to 8 ring carbons and preferably 5 to 7 ring carbons. The alkyl group and alkoxy group may be independently substituted with one or more members of the group including, but not limited to, mono-, di-,

25

30

tri-, or per-halogen, alkyl, alkoxy, aryl, heteroaryl, heterocyclyl, amino, substituted amino, OH, CN, mercapto, nitro, and C₁₋₈ acyloxy.

5 The term "acyl" as used herein, whether used alone or as part of a substituent group, means an organic radical having 2 to 6 carbon atoms (branched or straight chain) derived from an organic acid by removal of the hydroxyl group.

The term "Ac" as used herein means acetyl.

10 The term "halo" or "halogen" means fluoro, chloro, bromo and iodo. (Mono-, di-, tri-, and per-)halo-alkyl is an alkyl radical substituted by independent replacement of the hydrogen atoms thereon with halogen.

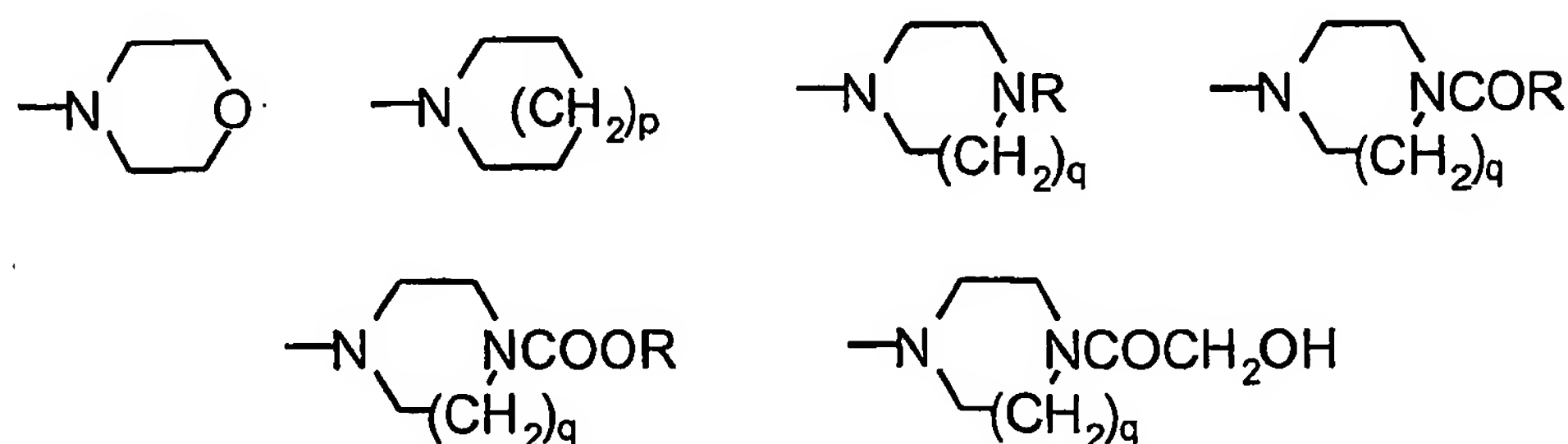
15 "Aryl" or "Ar," whether used alone or as part of a substituent group, is a carbocyclic aromatic radical including, but not limited to, phenyl, 1- or 2- naphthyl and the like. The carbocyclic aromatic radical may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with halogen, -OH, -CN, mercapto, nitro, amino, substituted amino, alkyl, -O-alkyl, -S-alkyl, -NH-alkyl, -N(alkyl)₂, (mono-, di-, tri-, and per-) halo-alkyl, formyl, -COR₅, -COOR₅, -CONHR₅,
20 -CONR₅R₆, -SOR₅, -SO₂R₅, -SO₂NHR₅, -SO₂NR₅R₆, alkyl-COO, alkyl-CONH, or carboxamide or a second aryl ring, wherein R₅ and R₆ are defined as hereinabove. Illustrative aryl radicals include, for example, phenyl, naphthyl, diphenyl, fluorophenyl, difluorophenyl, benzyl, benzoyloxyphenyl, carboethoxyphenyl, acetylphenyl, ethoxyphenyl, phenoxyphenyl, hydroxyphenyl,
25 carboxyphenyl, trifluoromethylphenyl, methoxyethylphenyl, acetamidophenyl, tolyl, xylyl, dimethylcarbamyphenyl and the like. "Ph" or "PH" denotes phenyl.

Whenever the term "alkyl", "acyl", or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkyl, dialkylamino) it shall be
30 interpreted as including those limitations given above for "alkyl", "acyl", and "aryl." Designated numbers of carbon atoms (e.g., C₁₋₈) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

Whether used alone or as part of a substituent group, "heteroaryl" refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O, and N; 0-2 ring atoms are additional heteroatoms independently selected from S, O, and N; and the remaining ring atoms are carbon. The radical being joined to the rest of the molecule via any of the ring atoms, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, triazolyl, oxadiazolyl, thienyl, furanyl, quinolinyl, isoquinolinyl, and the like. The heteroaryl group may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with halogen, -OH, -CN, mercapto, nitro, amino, substituted amino, alkyl, -O-alkyl, -S-alkyl, -NH-alkyl, -N(alkyl)₂, (mono-, di-, tri-, and per-)halo-alkyl, formyl, -COR₅, -COOR₅, -CONHR₅, -CONR₅R₆, -SOR₅, -SO₂R₅, -SO₂NHR₅, -SO₂NR₅R₆, alkyl-COO, alkyl-CONH, or carboxamide, wherein R₅ and R₆ are defined as hereinabove.

Heteroaryl may also be substituted with a mono-oxo to give 4-oxo-1H-quinoline and the like.

A "cyclic amino" derivative is a 4 to 8 membered nitrogen containing cyclic group where the other remaining members are selected from carbon, nitrogen, oxygen or sulfur, for instance an azetidiny group, pyrrolidinyl group, piperidinyl group, morpholino group, piperazinyl, or groups of the following formulae:



wherein p is -2 to 4 and q is 1-4.

25

"Heterocyclyl" or "heterocycle" is a 3- to 8-member saturated or partially saturated single or fused ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O and S. The heterocyclyl group may be attached at any heteroatom or carbon atom, which results in the creation of a

stable structure. Examples of heterocyclyl groups include, but are not limited to pyridine, pyrimidine, oxazoline, pyrrole, imidazole, morpholine, furan, indole, benzofuran, pyrazole, pyrrolidine, piperidine, and benzimidazole. "Heterocyclyl" or "heterocycle" may be substituted with one or more independent groups including, but not limited to, H, halogen, oxo, OH, alkyl, substituted alkyl, amino, substituted amino, carboxyl, alkylcarboxyl, and alkoxy.

Unless specified otherwise, it is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The compounds of the instant invention are asymmetric in the oxazolidinone ring at the 5- position and thus exist as optical antipodes. As such, all possible optical antipodes, enantiomers or diastereomers resulting from additional asymmetric centers that may exist in optical antipodes, racemates and racemic mixtures thereof are also part of this invention. The antipodes can be separated by methods known to those skilled in the art such as, for example, fractional recrystallization of diastereomeric salts of enantiomerically pure acids. Alternatively, the antipodes can be separated by chromatography on a Pirkle column.

The phrase "a pharmaceutically acceptable salt" denotes salts of the free base which possess the desired pharmacological activity of the free base and which are neither biologically nor otherwise undesirable. These salts may be derived from inorganic or organic acids. Examples of inorganic acids are hydrochloric acid, nitric acid, hydrobromic acid, sulfuric acid, or phosphoric acid. Examples of organic acids are acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid,

methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, methyl sulfonic acid, salicylic acid and the like. Suitable salts are furthermore those of inorganic or organic bases, such as KOH, NaOH, $\text{Ca}(\text{OH})_2$, $\text{Al}(\text{OH})_3$, piperidine, morpholine, ethylamine, triethylamine and the like.

5

Also included within the scope of the invention are the hydrated forms of the compounds which contain various amounts of water, for instance, the hydrate, hemihydrate and sesquihydrate forms.

10 The term "subject" includes, without limitation, any animal or artificially modified animal. As a particular embodiment, the subject is a human.

The term "drug-resistant" or "drug-resistance" refers to the characteristics of a microbe to survive in presence of a currently available antimicrobial agent
15 such as an antibiotic at its routine, effective concentration.

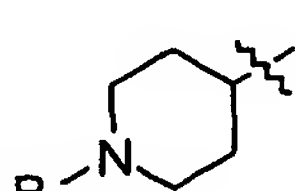
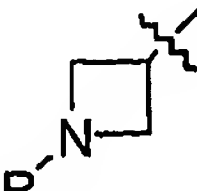
The compounds described in the present invention possess antibacterial activity due to their novel structure, and are useful as antibacterial agents for the treatment of bacterial infections in humans and animals.

20

In particular, compounds of Formula I wherein X is CH are embodiments of the present invention for such purposes.

Compounds of Formula I wherein R_2 is $\text{C}(\text{O})\text{R}_9$ wherein R_9 is as described
25 above are particular embodiments of this invention.

More particularly, compounds of Formula I wherein R_9 is H or alkyl are also embodiments of this invention.

30 Compounds of Formula I wherein R_1 is  or  wherein R_3 is as described above are further particular embodiments of this invention.

More particularly, compounds of Formula I wherein R_{2a} is H and R_3 is selected from $-\text{COR}_4$, $-\text{SO}_2\text{R}_9$ and $(\text{CH}_2)_t\text{heteroaryl}$ wherein R_4 , R_9 and t are as described above are embodiments of this invention.

5 Still more particularly, compounds of Formula I wherein R_4 is selected from OR_5 , $-(\text{CH}_2)_t\text{OR}_5$, alkyl, $-(\text{CH}_2)_t\text{aryl}$, and $-(\text{CH}_2)_t\text{heteroaryl}$ wherein R_5 and t are as described above are embodiments of this invention.

10 The following are yet other particular embodiments of the present invention for such purposes:

(S)-N-[[3-[3-fluoro-4-{N-(benzyloxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

15 (S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(methanesulfonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(methoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

20 (S)-N-[[3-[3-fluoro-4-{N-(2-pyrimidinyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(3-cyanobenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

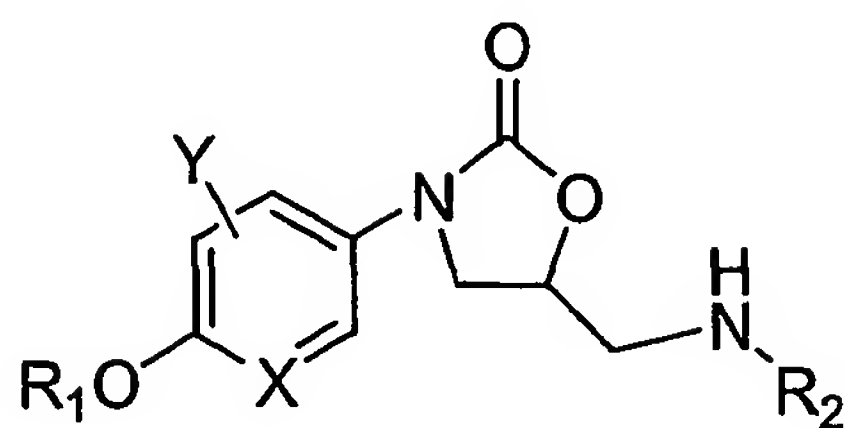
25 (S)-N-[[3-[3-fluoro-4-{N-(5-cyano-2-pyridyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(2-thienylcarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and

30 (S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

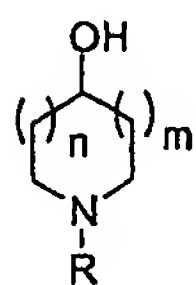
Finally, this invention provides a process for preparing a compound of Formula Ia



Formula Ia

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wherein R_1 is a moiety of the formula:

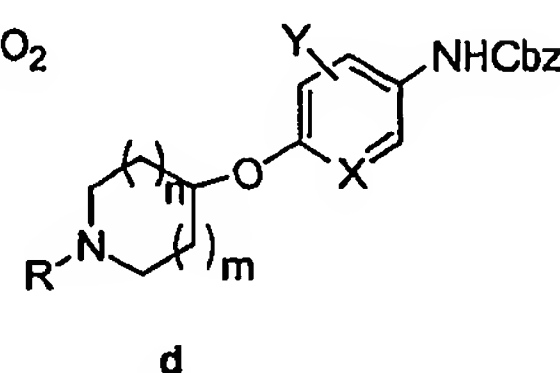
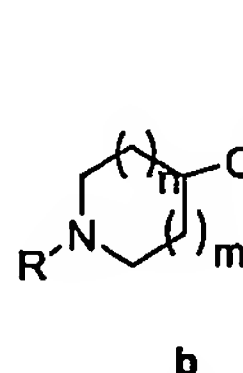
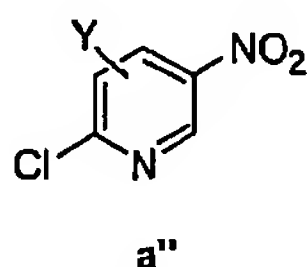
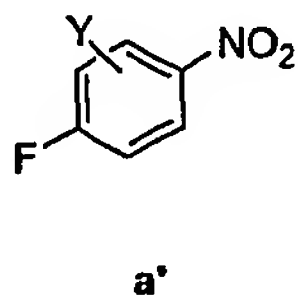
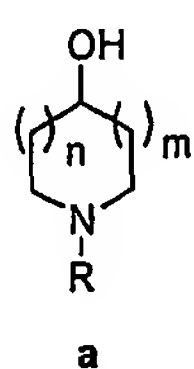


a wherein:

R is selected from Boc, $-\text{CH}(\text{Ph})_2$ or $-\text{COCH}_2\text{OCH}_2\text{Ph}$, n is 0, 1 or 2, m is 0 or 1, and R_2 , X, and Y are as described above, which process comprises:

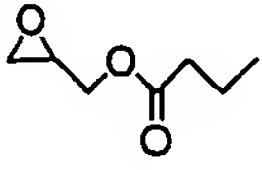
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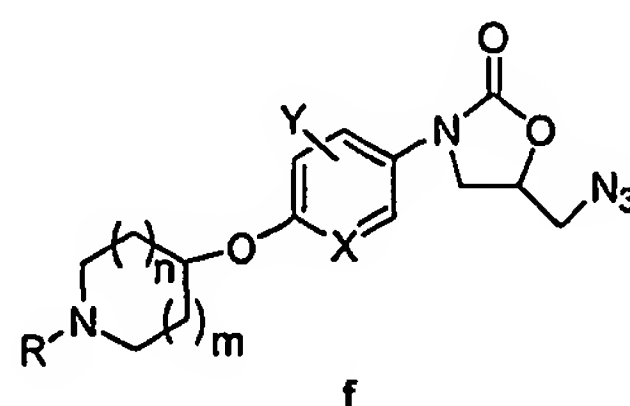
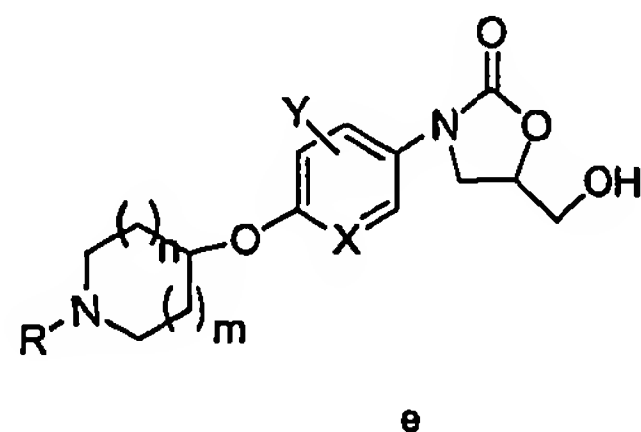
(a) reacting a compound of Formula a with a compound of Formula a' or a'' to form a compound of Formula b;



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(b) converting the compound of Formula b to a compound of Formula d;

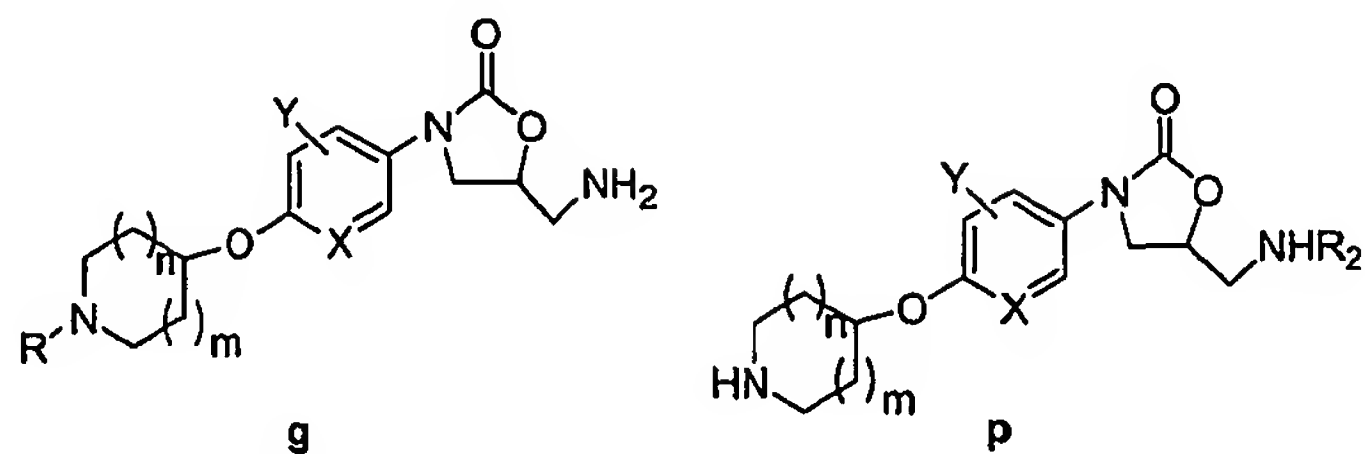
(c) reacting the compound of Formula d with  to form a compound of Formula e;



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(d) converting the compound of Formula e to a compound of Formula f;

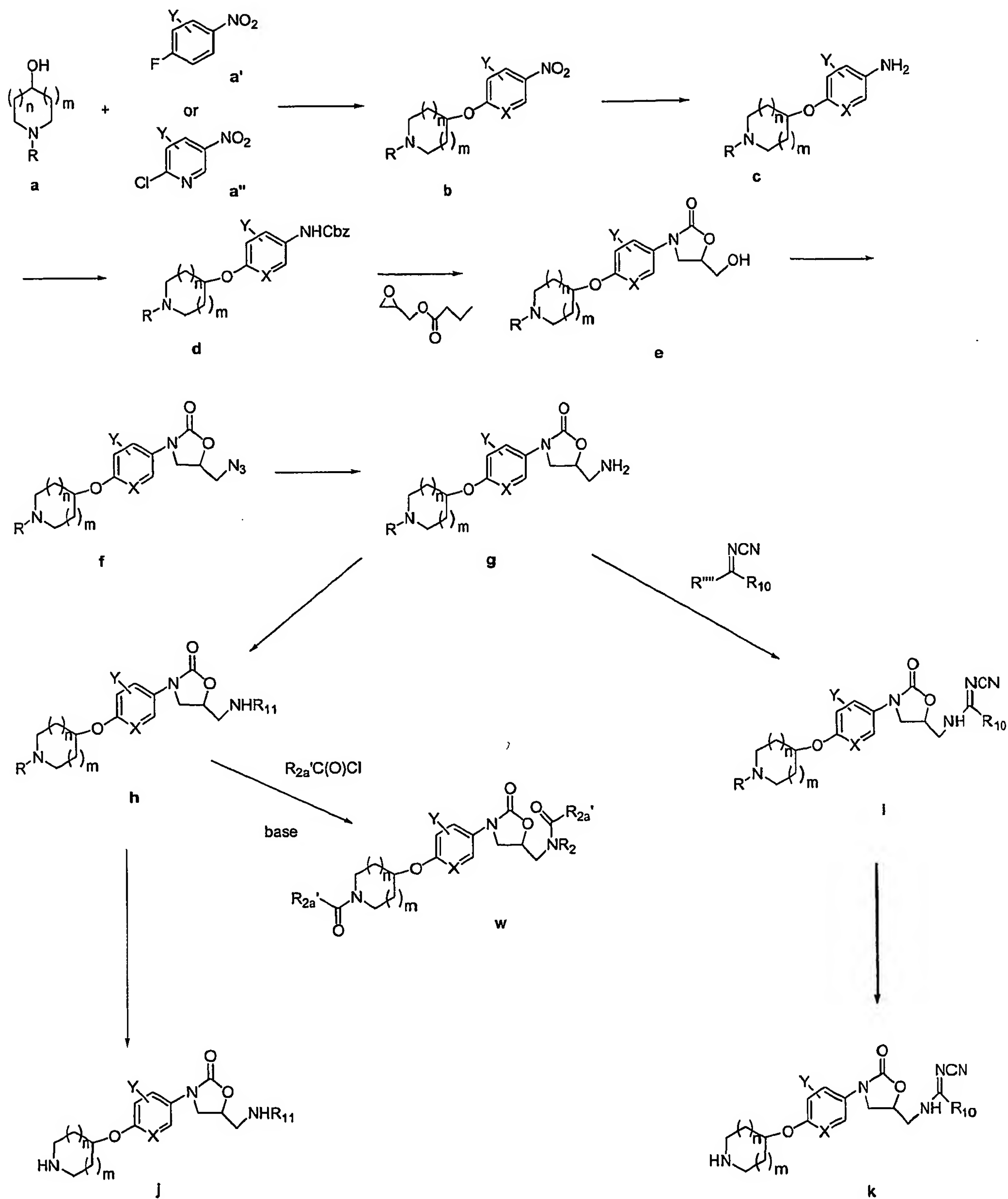
(e) converting the compound of Formula f to a compound of Formula g;



5 (f) converting the compound of Formula g to a compound of Formula p; and

(g) converting the compound of Formula p to a compound of Formula Ia.

10 The compounds of Formula I may be prepared from readily available starting materials such as known oxazolidinone intermediates in accordance with synthetic methods well known in the art. The following are representative procedures outlined in Schemes I and II:

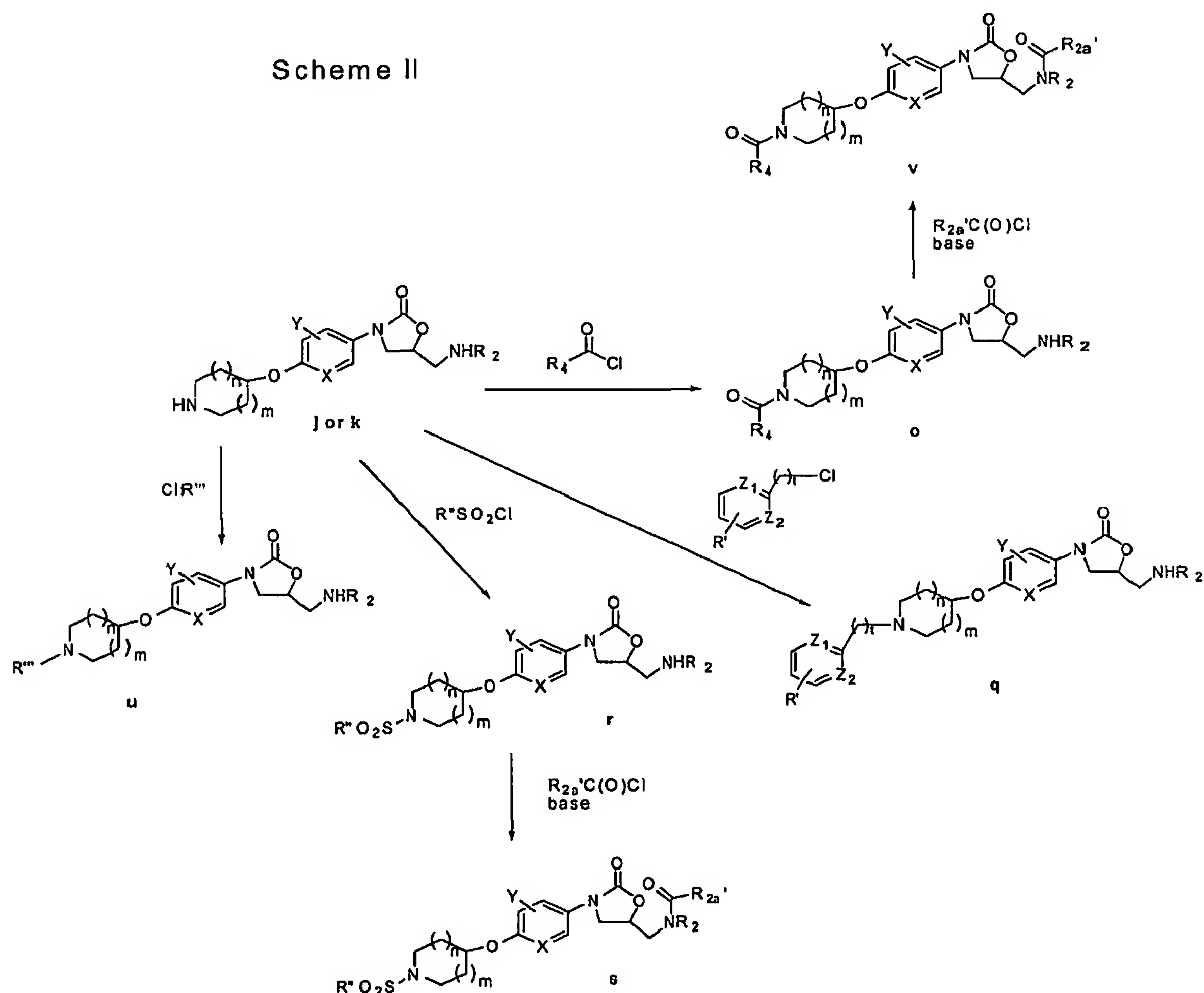


Scheme I

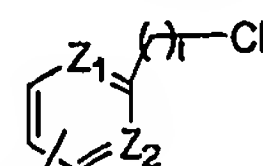
In accordance with Scheme I, wherein R is Boc, $-\text{CH}(\text{Ph})_2$ or $-\text{COCH}_2\text{OCH}_2\text{Ph}$, R_{11} is $-\text{COR}_9$ or $-\text{CO}_2\text{R}_9$, R' is any of the substituents on an aryl or heteroaryl group as described above, R'' is selected from R_9 and $-\text{NR}_5\text{R}_6$, R''' is selected from alkyl, substituted alkyl and $-\text{CHR}_5\text{R}_6$, R_{2a}' is optionally substituted alkyl, R'''' is $-\text{SCH}_3$ or $-\text{OCH}_3$, R_{10} is $-\text{NR}_9\text{R}_9$, R_9 , $-\text{SR}_9$, or $-\text{NHR}_9$, n is 0, 1 or 2 and m is 0 or 1, and X , Y , R_4 , R_5 , R_6 , R_9 , and t are as described above, an appropriately substituted halo-nitrobenzene such as that of Formula **a'** or an appropriately substituted halo-nitropyridine such as that of Formula **a''** is added to a compound of Formula **a** (all of which are either commercially available or may be readily prepared by known methods) in acetone, dimethylformamide (DMF), or tetrahydrofuran (THF). The mixture is treated with an appropriate base such as potassium t-butoxide (KOtBu) to obtain the corresponding compound of Formula **b**. The compound of Formula **b** may be reduced to the corresponding compound of Formula **c** under appropriate conditions such as H_2 , Pd/C and ethanol (EtOH) or NH_4OCOH , Pd/C and methanol (MeOH). Then compound **c** is treated with benzylchloroformate (CbzCl) in the presence of an appropriate base such as cesium carbonate (CsCO_3) in an appropriate solvent such as THF, H_2O or acetone to obtain the corresponding compound of Formula **d**. Compound **d** is then treated with an appropriate base such as $n\text{BuLi}$, followed by addition of glycidyl butyrate in an appropriate solvent such as THF to obtain the corresponding compound of Formula **e**. The compound of Formula **e** is treated with methanesulfonyl chloride (MsCl) and an appropriate base such as triethylamine (NEt_3) in an appropriate solvent such as methylene chloride (CH_2Cl_2). After standard workup, sodium azide (NaN_3) is then added into the mixture in an appropriate solvent such as dimethylformamide (DMF) and heated at a preferred temperature range of 70°C to 90°C to obtain the corresponding compound of Formula **f**. The compound of Formula **f** may be reduced under appropriate conditions such as H_2 and Pd/C in an appropriate solvent such as ethyl acetate (EtOAc), or the compound of Formula **f** may be reduced using triphenylphosphine (PPh_3) and THF/ H_2O to obtain the corresponding compound of Formula **g**.

The compound of Formula **g** can be treated with an appropriate acylating agent such as acetic anhydride (Ac_2O) or acetyl chloride (AcCl), along with an appropriate base such as pyridine or NEt_3 to give the corresponding compound of Formula **h**. The compound of Formula **g** can also be treated with an appropriate imidate to give the corresponding compound of Formula **i**. Compound **h** wherein **R** is $-\text{CH}(\text{Ph})_2$ can be converted to the corresponding compound of Formula **w** by reacting with $\text{R}_{2a}'\text{C}(\text{O})\text{Cl}$ in the presence of a base such as TEA. Compounds **j** and **k** can be obtained from compounds **h** and **i**, respectively, by deprotection with either trifluoroacetic acid (TFA) in an appropriate solvent such as CH_2Cl_2 or with Pd/C in an appropriate solvent such as EtOH or EtOAc.

Compounds of Formulae **o**, **q**, **r**, **s**, and **u** may be obtained in accordance with different routes as shown in Scheme II:



The compound of Formula j or k can be treated with an appropriate alkylating agent represented by ClR''' in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula u. Alternatively, the compound of Formula j or k can be treated with an appropriate sulfonyl chloride represented by $\text{R}''\text{SO}_2\text{Cl}$ such as MsCl in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula r. Still alternatively, the compound of Formula j or k can be treated



with an appropriate alkylating agent represented by R' , wherein Z_1 and Z_2 are independently N or CH, in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula q. In addition, the compound of Formula j or k can also be treated with an appropriate acylating agent represented by R_4COCl such as AcCl in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula o. In several cases, R_4 contains a protected amine or protected alcohols moiety. After removal of the protecting group, the resulting amine or alcohol can be further derivatized. Compounds of Formulae o and r can be converted to compounds of Formulae v and s, respectively, by reacting with $\text{R}_{2a}'\text{C}(\text{O})\text{Cl}$ in the presence of a base such as TEA.

These compounds have antimicrobial activity against susceptible and drug resistant *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *E. faecalis*, *E. faecium*, *Moraxella catarrhalis* and *H. influenzae*. These compounds are particularly useful against drug resistant Gram positive cocci such as methicillin-resistant staphylococci and vancomycin-resistant enterococci. These compounds are useful in the treatment of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital-acquired lung infections, bone and joint infections, and other bacterial infections.

Minimal inhibitory concentration (MIC) has been an indicator of in vitro antibacterial activity widely used in the art. The in vitro antimicrobial activity of the

compounds was determined by the microdilution broth method following the test method from the National Committee for Laboratory Standards (NCCLS). This method is described in the NCCLS Document M7-A4, Vol.17, No.2, "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically--Fourth Edition", which is incorporated herein by reference.

In this method two-fold serial dilutions of drug in cation adjusted Mueller-Hinton broth are added to wells in microdilution trays. The test organisms are prepared by adjusting the turbidity of actively growing broth cultures so that the final concentration of test organism after it is added to the wells is approximately 5×10^4 CFU/well.

Following inoculation of the microdilution trays, the trays are incubated at 35 °C for 16-20 hours and then read. The MIC is the lowest concentration of test compound that completely inhibits growth of the test organism. The amount of growth in the wells containing the test compound is compared with the amount of growth in the growth-control wells (no test compound) used in each tray. As set forth in Table 1, compounds of the present invention were tested against a variety of Gram positive and Gram negative pathogenic bacteria resulting in a range of activities, from 1 to ≥ 128 $\mu\text{g/mL}$ depending on the organism tested.

Table 1. MIC Values of Some Compounds of Formula I

Com- pound No.	MIC ($\mu\text{g/mL}$)			Com- pound No.	MIC ($\mu\text{g/mL}$)		
	<i>E. faecium</i> OC3312	MRSA OC 2878	<i>S. aureus</i> Broth		<i>E. faecium</i> OC3312	MRSA OC 2878	<i>S. aureus</i> Broth
1	>32	16	32	32	32	8	16
2	8	32	8	33	32	16	16
3	4	2	4	34	>128	64	128
4	8	4	4	35	64	32	32
5	16	8	8	36	16	8	8
6	8	4	4	37	16	8	8
7	16	8	8	38	32	8	16
8	8	4	8	39	16	16	16
9	8	4	4	40	16	8	4
10	32	16	16	41	>128	64	128
11	16	8	16	42	>128	32	32
12	16	8	8	43	>128	128	128
13	16	8	8	44	128	64	32
14	8	4	4	45	128	64	64
15	8	8	8	46	>128	64	64
16	32	32	32	47	>128	64	64
17	16	16	8	48	>128	32	64
18	64	16	8	49	>128	128	> 64
19	32	32	16	50	>64	64	>64
20	16	8	8	51	8	8	16
21	64	32	32	52	4	8	8
22	8	4	8	53	16	8	8
23	16	4	16	54	8	8	8
24	32	16	8	55	8	16	16
25	64	32	32	56	32	32	32
26	16	8	16	57	16	16	16
27	16	16	16	58	4	4	8
28	16	8	16	59	16	8	4
29	32	16	32	60	>128	16	8
30	16	8	16	61	128	64	32
31	32	16	16				

5 This invention further provides a method of treating bacterial infections, or enhancing or potentiating the activity of other antibacterial agents, in warm-blooded animals, which comprises administering to the animals a compound of the invention alone or in admixture with another antibacterial agent in the form of a medicament according to the invention.

When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, e.g., solvents, diluents, and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing for example, 5 from about 0.5% to 5% of suspending agent, syrups containing, for example, from about 10% to 50% of sugar, and elixirs containing, for example, from about 20% to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.5% to 5% suspending agent in an isotonic medium. These pharmaceutical preparations may contain, for 10 example, from about 0.5% up to about 90% of the active ingredient in combination with the carrier, more usually between 5% and 60% by weight.

Compositions for topical application may take the form of liquids, creams or gels, containing a therapeutically effective concentration of a compound of the 15 invention admixed with a dermatologically acceptable carrier.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid 20 carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring 25 agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and 30 hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred. These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacological acceptable salt can be prepared in water suitably mixed

with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

5

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

15

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg/kg to about 400 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 0.07 g to 7.0 g, preferably from about 100 mg to 1000 mg. Dosage forms suitable for internal use comprise from about 100 mg to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

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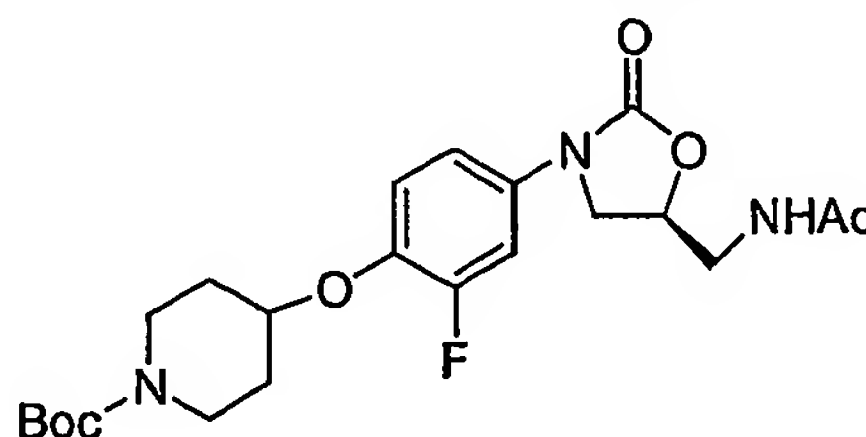
The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical

composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

The following examples describe in detail the chemical synthesis of representative compounds of the present invention. The procedures are illustrations, and the invention should not be construed as being limited by chemical reactions and conditions they express. No attempt has been made to optimize the yields obtained in these reactions, and it would be obvious to one skilled in the art that variations in reaction times, temperatures, solvents, and/or reagents could increase the yields.

Example 1

(S)-N-[[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 1

N-(*t*-Butoxycarbonyl)-4-piperidinol:

To a solution of 25 g (247 mmol) 4-piperidinol in 350 mL dry tetrahydrofuran (THF) at 0°C was added dropwise 60.2 g (276 mmol) di-*t*-butylcarbonate in 350 mL dry THF. The reaction was allowed to warm to room temperature (rt) and stirred overnight. The solvent was removed under reduced pressure, the resulting residue dissolved in 700 mL CH₂Cl₂ and the solution extracted with H₂O (1 x 400 mL), dried over MgSO₄, filtered and rotary evaporated to yield 45 g (91%) of N-(*t*-butoxycarbonyl)-4-piperidinol as an oil which slowly solidified to white crystals. ¹H NMR (CDCl₃) δ 3.75-3.96 (m, 3H); 2.92-3.13 (m, 2H); 1.80-1.93 (m, 4H); and 1.48 (s, 9H).

1-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-nitrobenzene:

To a solution of 740 mg (3.7 mmol) of N-(*t*-butoxycarbonyl)-4-piperidinol in 10 mL dry THF at 0°C was added dropwise 4 mL (4.0 mmol) 1M KO^tBu. After stirring at 0°C for 0.5 h, 0.40 mL (3.6 mmol) 3,4-difluoronitrobenzene was added and the reaction warmed to rt and stirred overnight. The reaction was poured into 100 mL H₂O and extracted with CH₂Cl₂ (3 x 100 mL). The combined aqueous layers were washed with H₂O, dried with MgSO₄, filtered, and the solvent removed by rotary evaporation. Then the solid was triturated with cold hexanes to afford 1.1 g (89%) of 1-[N-(*t*-butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-nitrobenzene as a pale yellow solid; mp 88-90°C, MS (CI) [M+Na]⁺ 364.

1-[4-(N-*t*-Butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-aminobenzene:

To 1.78 g (5.23 mmol) of 1-[N-(*t*-butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-nitrobenzene in 100 mL MeOH was added 1.05 g (16.6 mmol) ammonium formate and 70 mg 10% Pd/C and the reaction heated at reflux under N₂ for 2 h. The reaction was filtered through a pad of celite and the filtrate evaporated to afford crude aniline as a gold oil. The material was used without further purification in the next step.

2-Fluoro-1-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}-4-(phenylmethoxycarbonylamino)benzene:

To 1-[4-(N-*t*-butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-aminobenzene (5.23 mmol) in 150 mL 2:1 acetone:H₂O at 0°C was added 1.03 g (12.3 mmol) NaHCO₃ and 0.90 mL (6.30 mmol) benzylchloroformate. After stirring at rt for 6 h the volatiles were evaporated, the residue diluted with 300 mL H₂O and extracted with Et₂O (3 x 150 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (20% EtOAc in Hexanes) afforded 2.06 g (89%) of 2-fluoro-1-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}-4-(phenylmethoxycarbonylamino)benzene as a yellow, waxy solid. ¹H NMR (CDCl₃) δ 7.3-7.4 (m, 6H); 6.9-7.0 (m, 2H); 6.60 (brs, 1H); 4.3-4.4 (m, 1H); 3.7-3.8 (m, 2H); 3.2-3.3 (m, 2H); 1.8-2.0 (m, 2H); 1.6-1.8 (m, 2H); and 1.48 (s, 9H).

(R)-[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol:

To 1.73 g (3.89 mmol) of 2-fluoro-1-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}-4-(phenylmethoxycarbonylamino)benzene in 25 mL dry THF at -78 °C was
5 added 2 mL (5.0 mmol) 2.5M *n*-BuLi and the reaction stirred for 1 h. Then 0.71 mL (5.01 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred overnight. The reaction was carefully poured into 150 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent
10 removed by rotary evaporation. Silica gel chromatography (40% EtOAc in hexanes to 70% EtOAc in hexanes) gave 1.15 g (72%) of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol as a white solid; mp 110-111°C, MS (CI) [M+Na]⁺ 433.5.

15 (R)-[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

To 1.03 g (2.51 mmol) of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol in 50 mL CH₂Cl₂ at 0°C was added 0.70 mL (5.02 mmol) NEt₃ and 0.37 mL (4.78 mmol) methanesulfonyl chloride.
20 After stirring for 3 h at 0°C the reaction was poured into 75 mL H₂O and extracted with CH₂Cl₂ (100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered and the solvent removed by rotary evaporation to yield 1.21 g (99%) of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate as a cream solid; mp 127-129°C, MS (CI)
25 [M+H-Boc]⁺ 389.2.

(R)-[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate (5.20 mmol) in 70 mL
30 dimethylformamide (DMF) was added 1.22 g (18.8 mmol) sodium azide and the reaction heated at 75°C overnight. Then the reaction was poured into 300 mL H₂O and extracted with EtOAc (3 x 200 mL). The combined organic layers were

washed with H₂O (3 x 200 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 2.07 g (92%) of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide as a beige solid. ¹H NMR (CDCl₃) δ 7.46 (dd, *J* = 12.9 and 2.7 Hz, 1H); 7.14 (dt, *J* = 8.9 and 1.4 Hz, 1H); 7.01 (t, *J* = 8.9 Hz, 1H); 4.7-4.8 (m, 1H); 4.3-4.4 (m, 1H); 4.05 (t, *J* = 8.9 Hz, 1H); 3.83 (dd, *J* = 8.9 and 6.2 Hz, 1H); 3.7-3.8 (m, 2H); 3.71 (dd, *J* = 13.2 and 4.6 Hz, 1H); 3.59 (dd, *J* = 13.2 and 4.3 Hz, 1H); 3.2-3.3 (m, 2H); 1.8-2.0 (m, 2H); 1.7-1.8 (m, 2H); and 1.47 (s, 9H).

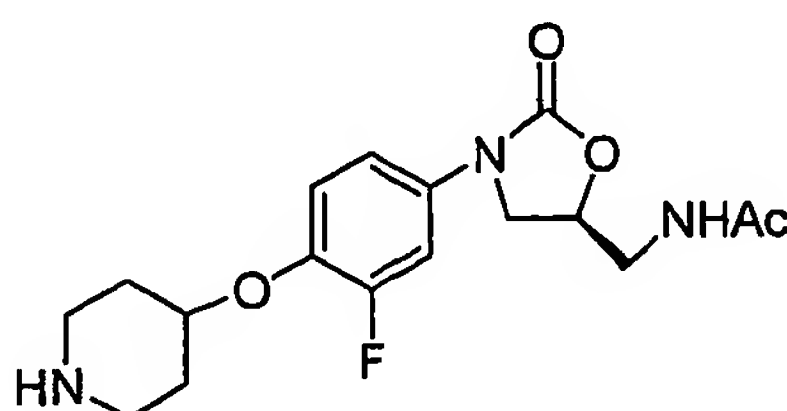
10 (S)-N-[[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 1):

To a solution of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide (5.20 mmol) in 9 mL dry THF was added 1.51 g (5.75 mmol) triphenylphosphine and the reaction stirred for 3 h at rt. Then 4.5 mL H₂O was added and the reaction heated at 60°C for 4 h. The volatiles were evaporated and the residue azeotroped with benzene (2 x 20 mL) to yield the crude amine.

To a solution of this crude amine in 100 mL EtOAc was added 0.58 mL (6.15 mmol) acetic anhydride and 1.2 mL (14.8 mmol) pyridine, and the reaction stirred at rt overnight. The reaction mixture was poured into 250 mL H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Silica gel chromatography (100% EtOAc to 5% MeOH in EtOAc) yielded 1.85 g (79%) of (S)-N-[[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 179-180°C, MS (CI) [M+Na]⁺ 474.

Example 2

(S)-N-[[3-[3-Fluoro-4-{piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

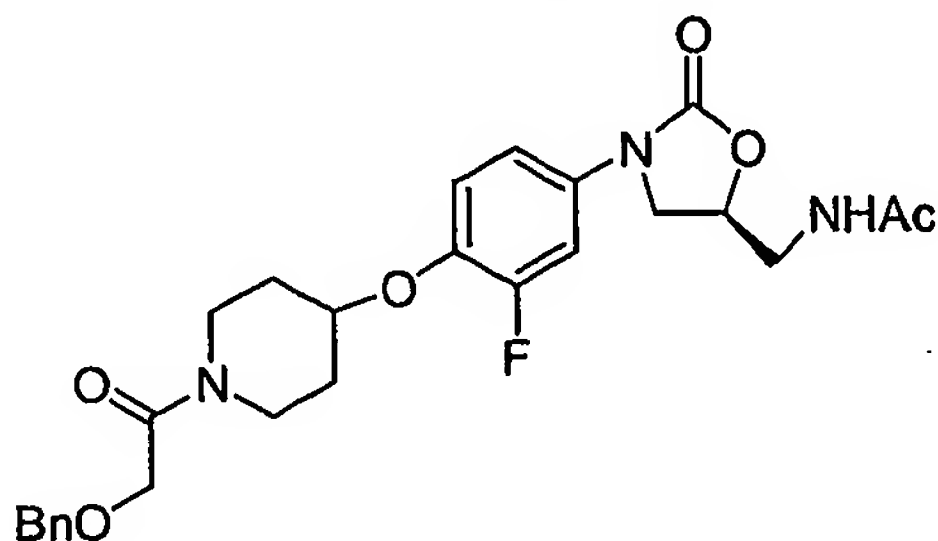


Compound 2

To a solution of 1.94 g (4.30 mmol) of Compound 1 in 225 mL CH₂Cl₂ was added 2.5 mL (32.5 mmol) trifluoroacetic acid (TFA) and the reaction stirred at rt. for 6 h. The volatiles were evaporated under reduced pressure. The resulting oil (TFA salt) was dissolved in 100 mL H₂O, extracted with EtOAc (100 mL), and the aqueous layer was cooled to 0°C and basicified with 1N NaOH. This solution was extracted with EtOAc (5 x 200 mL), the combined extracts washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure to yield (S)-N-
10 [[3-[3-fluoro-4-{piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a pale yellow glass; mp 55-59°C, MS (CI) [M+H]⁺ 352.

Example 3

(S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide
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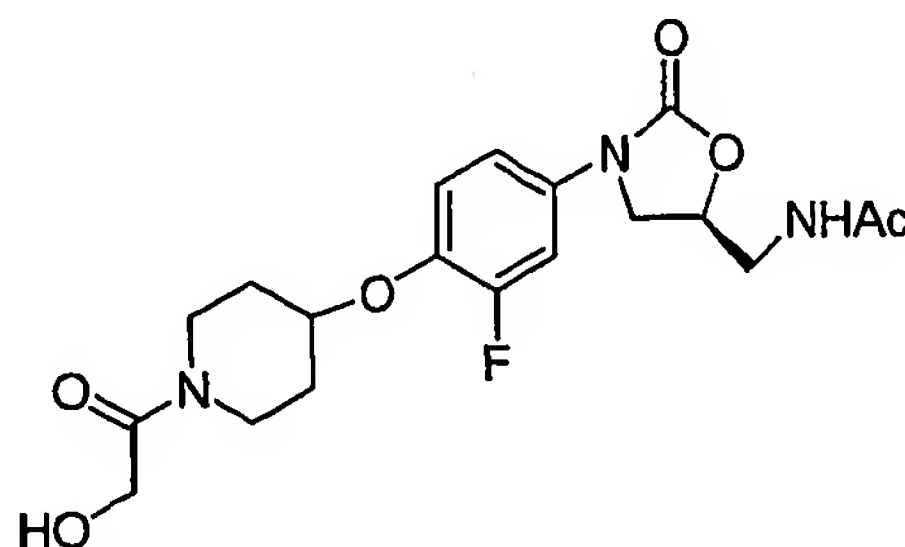


Compound 3

To a suspension of Compound 2 (1.50 mmol) in 50 mL CH₂Cl₂ was added 0.60 mL (4.3 mmol) NEt₃ and 0.25 mL (1.58 mmol) benzyloxyacetyl chloride. After stirring for 18 h, the reaction was poured into 75 mL H₂O and extracted with CH₂Cl₂ (4 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure. Silica gel chromatography (5% MeOH in EtOAc) afforded (S)-N-[[3-[3-fluoro-4-{N-(benzyloxyacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide as a white glass. ¹H NMR (CDCl₃) δ 7.47 (dd, J = 12.9 and 2.5 Hz, 1H); 7.2-7.4 (m, 6H); 6.98 (t, J = 8.8 Hz, 1H); 6.24 (brt, J = 6.1 Hz, 1H); 4.7-4.8 (m, 1H); 4.61 (s, 2H); 4.4-4.5 (m, 1H); 4.20 (s, 2H); 4.02 (t, J = 9.0 Hz, 1H); 3.6-3.8 (m, 6H); 3.4-3.5 (m, 1H); 2.02 (s, 3H); and 1.8-1.9 (m, 4H).

Example 4

(S)-N-[[3-[3-Fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-4-oxy}phenyl]-
2-oxo-5-oxazolidinyl]methyl]acetamide

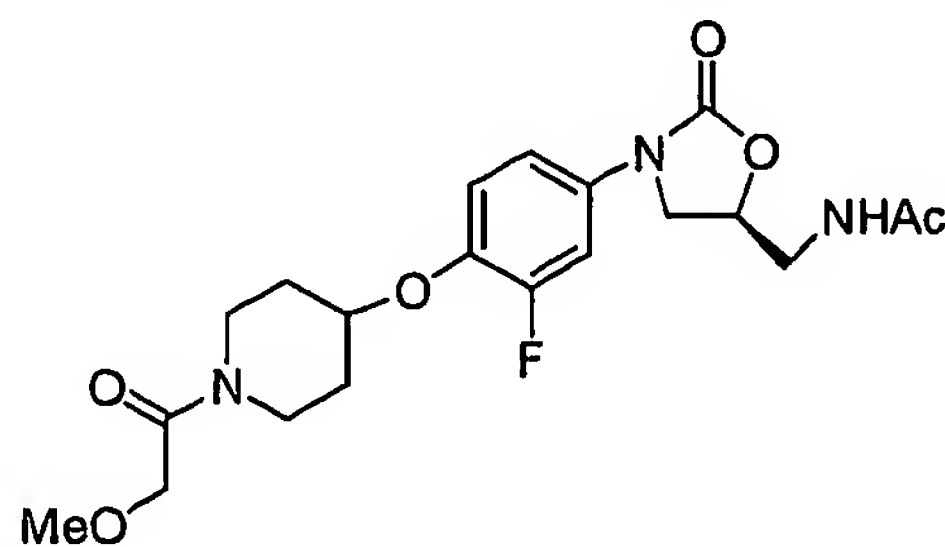


Compound 4

To a solution of 540 mg (1.08 mmol) of Compound 3 in 50 mL MeOH was added 503 mg ammonium formate and a catalytic amount of 10% Pd/C, and the reaction was heated at reflux overnight. Then the reaction was filtered through a pad of celite and the solvent removed under reduced pressure. Silica gel chromatography (2% to 10% MeOH in CH₂Cl₂) afforded (S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetamide)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetyl as a hygroscopic white foam (93%). ¹H NMR (CDCl₃) δ 7.49 (dd, J = 12.9 and 2.6 Hz, 1H); 7.09 (dd, J = 8.9 and 1.6 Hz, 1H); 7.00 (t, J = 8.9 Hz, 1H); 6.18 (brt, J = 6.1 Hz, 1H); 4.7-4.8 (m, 1H); 4.51 (q, J = 4.6 Hz, 1H); 4.19 (s, 2H); 4.02 (t, J = 9.0 Hz, 1H); 3.5-3.8 (m, 7H); 3.20 (dt, J = 13.7 and 5.2 Hz, 1H); 2.03 (s, 3H); and 1.90 (m, 4H).

Example 5

(S)-N-[[3-[3-Fluoro-4-{N-(methoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

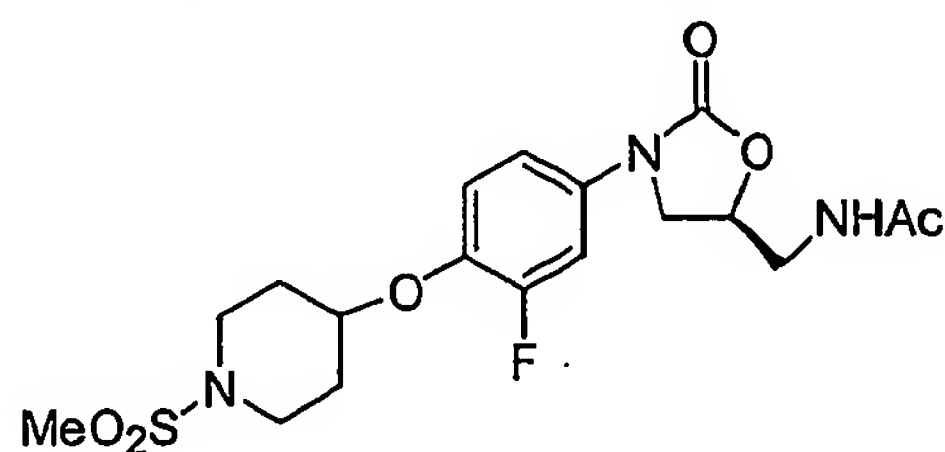


Compound 5

To a solution of (S)-N-[[3-[3-fluoro-4-{piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.756 mmol) in 30 mL EtOAc was added 1.0 mL (7.17 mmol) NEt₃ and methoxyacetylchloride (0.875 mmol). The reaction stirred at rt for 2.5 h, was poured into 50 mL H₂O, and extracted with EtOAc. The organic layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the impure amide. Silica gel chromatography (2.5 to 10% MeOH in CH₂Cl₂) afforded 101 mg (32%) of (S)-N-[[3-[3-fluoro-4-{N-(methoxyacetyl) piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a beige foam. ¹H NMR (CDCl₃) δ 7.48 (dd, J = 12.9 and 2.5 Hz, 1H); 7.10 (m, 1H); 7.00 (t, J = 8.8 Hz, 1H); 6.00 (brt, 1H); 4.77 (m, 1H); 4.46 (m, 1H); 4.13 (s, 2H); 4.03 (t, J = 8.9 Hz, 1H); 3.5-3.8 (m, 6H); 3.44 (s, 3H); 3.43 (m, 1H); 2.03 (s, 3H); and 1.7-1.9 (m, 4H).

Example 6

(S)-N-[[3-[3-Fluoro-4-{N-(methanesulfonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

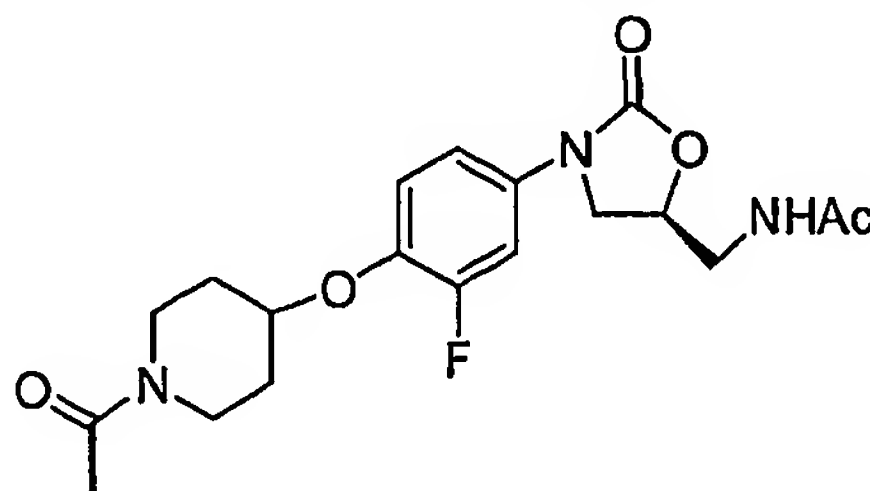


Compound 6

To a solution of 115 mg (0.33 mmol) of Compound 2 in 5 mL CH₂Cl₂ was added 0.05 mL (0.36 mmol) NEt₃ and 0.03 mL (0.39 mmol) methanesulfonyl chloride. The reaction stirred at rt for 22 h, was poured into 50 mL H₂O, and extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the impure sulfonamide. The sulfonamide was purified by dissolving in EtOAc, washing with sat. NaHCO₃, drying over MgSO₄, and removal of the solvent under reduced pressure to give (S)-N-[[3-[3-fluoro-4-{N-(methanesulfonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 123-125°C, MS (CI) [M+H]⁺ 430.

Example 7

(S)-N-[[3-[3-Fluoro-4-{N-(acetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 7

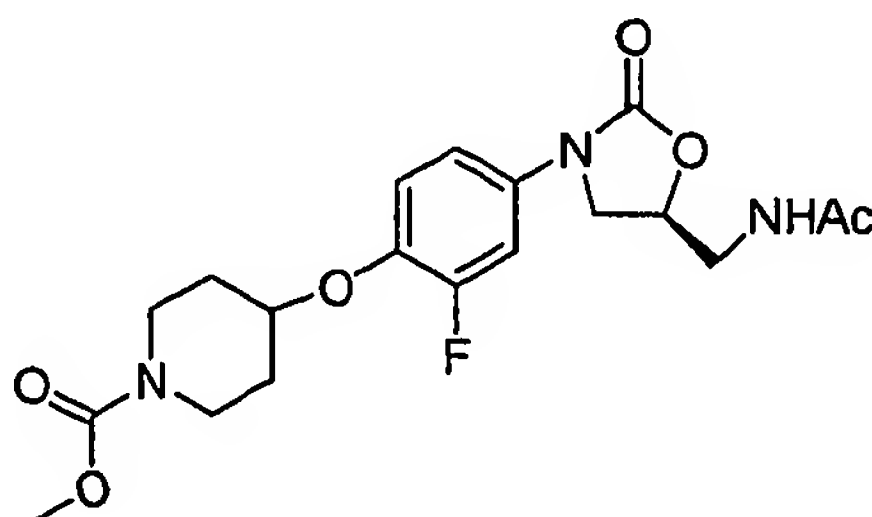
5

To a solution of 155 mg (0.44 mmol) of Compound 2 in 30 mL CH₂Cl₂ was added 0.10 mL (0.72 mmol) NEt₃ and 0.05 mL (0.70 mmol) acetyl chloride. The reaction stirred at rt for 18 h, was poured into 50 mL H₂O, and extracted with
 10 CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the impure amide. The amide was purified by dissolving in EtOAc, washing with sat. NaHCO₃, drying over MgSO₄, and the solvent removed under reduced pressure to give (S)-N-[[3-
 15 [3-fluoro-4-{N-(acetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. ¹H NMR (CDCl₃) δ 7.47 (dd, *J* = 12.9 and 2.2 Hz, 1H); 7.06 (m, 2H); 6.97 (brt, *J* = 8.8 Hz, 1H); 4.79 (m, 1H); 4.46 (m, 1H); 4.03 (t, *J* = 9.0 Hz, 1H); 3.6-3.8 (m, 6H); 3.52 (m, 1H); 2.12 (s, 3H); 2.02 (s, 3H); and 1.88 (m, 4H).

20

Example 8

(S)-N-[[3-[3-Fluoro-4-{N-(methoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



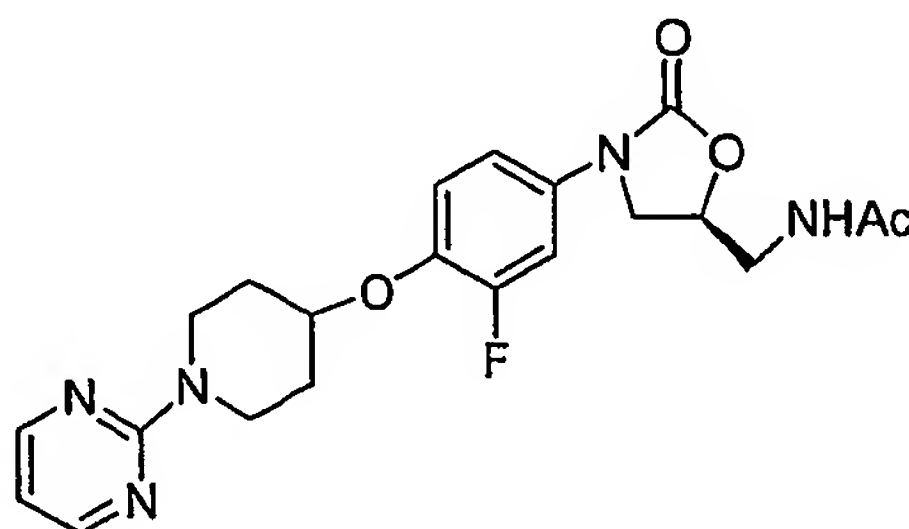
Compound 8

25

To a solution of 201 mg (0.57 mmol) of Compound 2 in 50 mL EtOAc was added 0.15 mL NEt₃ and 0.10 mL methylchloroformate. The reaction stirred at rt for 20 h, was poured into 50 mL H₂O, and extracted with EtOAc. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 167 mg (72%) of (S)-N-[[3-[3-fluoro-4-{N-(methoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid. ¹H NMR (CDCl₃) δ 7.47 (m, 1H); 7.26 (m, 1H); 7.06 (m, 1H); 6.03 (m, 1H); 4.78 (m, 1H); 4.41 (m, 1H); 4.02 (t, J = 8.9 Hz, 1H); 3.71 (s, 3H); 3.6-3.7 (m, 5H); 3.41 (m, 2H); 2.02 (s, 3H); 1.89 (m, 2H); and 1.79 (m, 2H).

Example 9

(S)-N-[[3-[3-Fluoro-4-{N-(2-pyrimidinyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

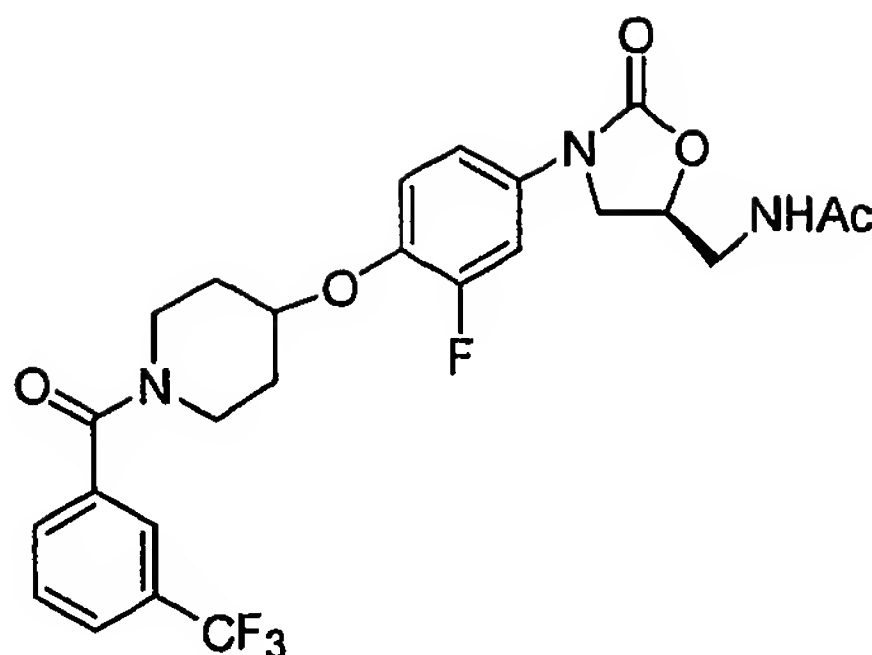


Compound 9

To a solution of 176 mg (0.50 mmol) of Compound 2 in 7.5 mL EtOH was added 0.23 mL NEt₃ and 61 mg (0.53 mmol) 2-chloropyrimidine and the reaction heated at reflux for 21 h. After cooling, the reaction was poured into 50 mL sat. NaHCO₃, and extracted with CH₂Cl₂ (4 x 50 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 174 mg (81%) of (S)-N-[[3-[3-fluoro-4-{N-(2-pyrimidinyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 121-123°C, MS (CI) [M+H]⁺ 430.

Example 10

(S)-N-[[3-[3-Fluoro-4-{N-(3-trifluoromethylbenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

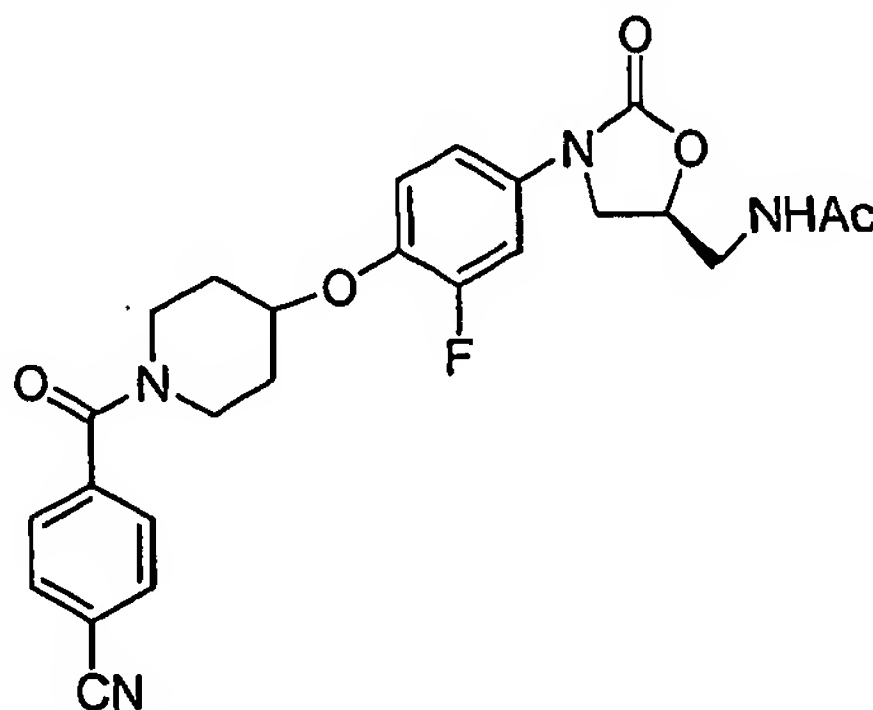


Compound 10

To a solution of 101 mg (0.29 mmol) of Compound 2 in 10 mL CH₂Cl₂ was added 260 mg AMBERLYST 21 Basic Resin and 1.0 mL (6.6 mmol) 3-trifluoromethylbenzoyl chloride and the reaction shaken for 3.5 h at rt. Then 2.4 g P-trisamine was added and the reaction shaken overnight. The reaction was filtered and the resin washed with CH₂Cl₂. The combined organic layers were washed with sat. NaHCO₃, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the crude amide. The amide was triturated with hexanes 3 times to afford 100 mg (67%) of (S)-N-[[3-[3-fluoro-4-{N-(3-trifluoromethylbenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white powder; mp 150-152°C, MS (CI) [M+H]⁺ 524.

Example 11

(S)-N-[[3-[3-Fluoro-4-{N-(4-cyanobenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



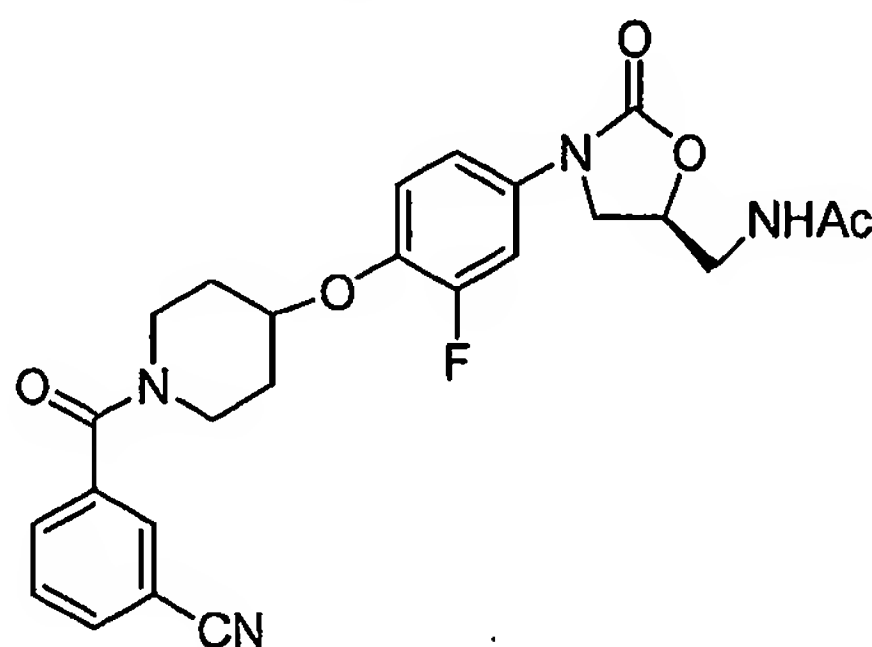
Compound 11

To a solution of 51 mg (0.15 mmol) of Compound 2 in 7.5 mL CH₂Cl₂ was added 207 mg AMBERLYST 21 Basic Resin and 116 mg (0.70 mmol) 4-

cyanobenzoyl chloride and the reaction was shaken for 18 h at rt. Then 250 mg P-trisamine was added and the reaction was shaken for 20 h. The reaction was filtered and the resin washed with CH₂Cl₂. The organic solvent was removed by rotary evaporation to yield 63 mg (91%) of (S)-N-[[3-[3-fluoro-4-{N-(4-cyanobenzoyl)piperidiny-4-oxo}phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 75-78°C, MS (CI) [M+H]⁺ 481.

Example 12

(S)-N-[[3-[3-Fluoro-4-{N-(3-cyanobenzoyl)piperidiny-4-oxo}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

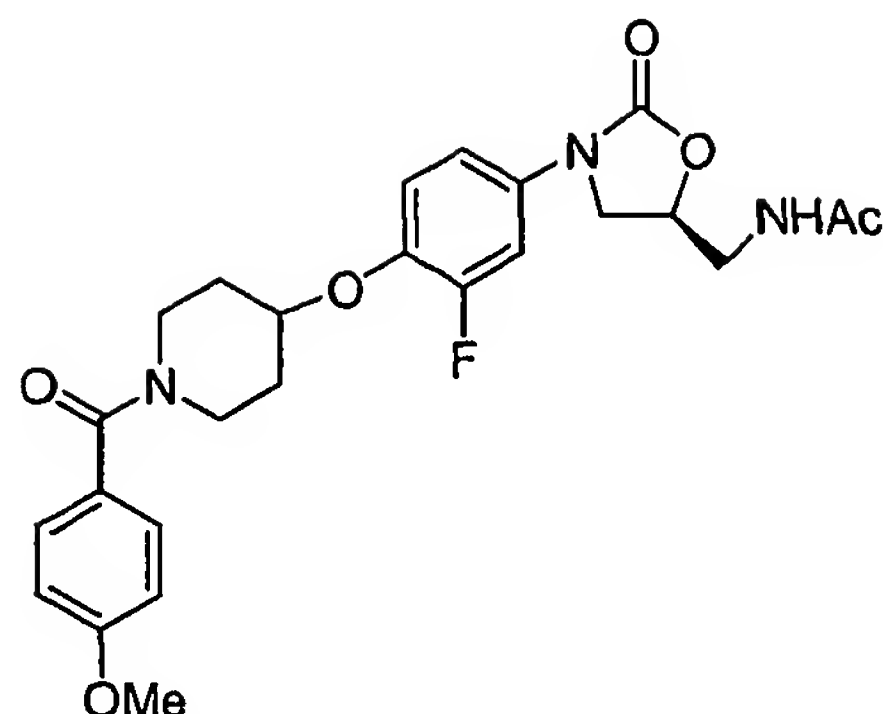


Compound 12

To a solution of 75 mg (0.21 mmol) of Compound 2 in 7.5 mL CH₂Cl₂ was added 200 mg AMBERLYST 21 Basic Resin and 128 mg (0.77 mmol) 3-cyanobenzoyl chloride and the reaction was shaken for 18 h at rt. Then 300 mg P-trisamine was added and the reaction was shaken for 20 h. The reaction was filtered and the resin washed with CH₂Cl₂. The organic solvent was removed by rotary evaporation to yield 103 mg (100%) of (S)-N-[[3-[3-fluoro-4-{N-(3-cyanobenzoyl)piperidiny-4-oxo}phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 82-85°C, MS (CI) [M+H]⁺ 481.

Example 13

(S)-N-[[3-[3-Fluoro-4-{N-(4-methoxybenzoyl)piperidiny-4-oxo}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



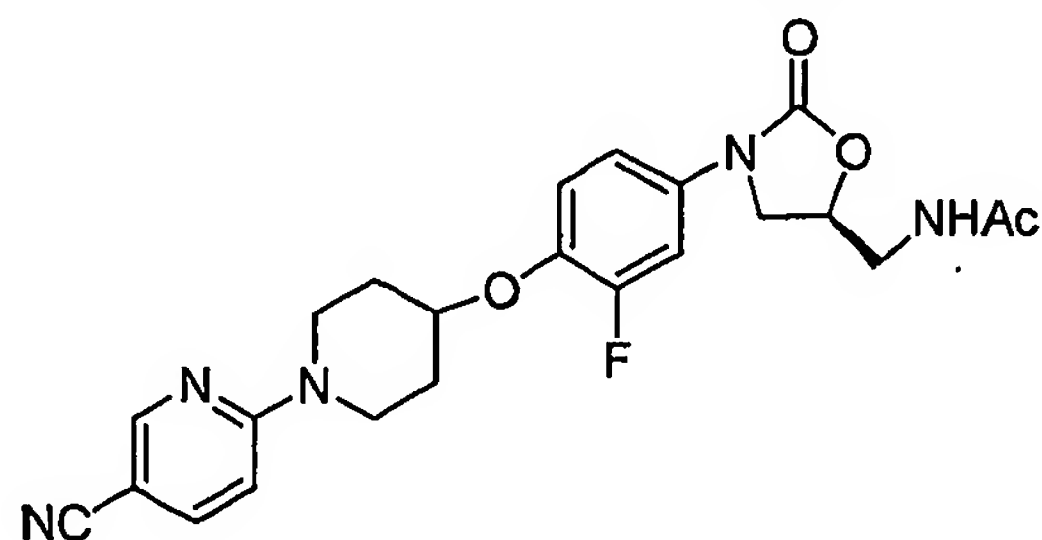
Compound 13

To a solution of 133 mg (0.29 mmol) of Compound 2 in 10 mL CH₂Cl₂ was added 350 mg AMBERLYST 21 Basic Resin and 255 mg (1.49 mmol) *p*-anisoyl chloride and the reaction was shaken for 3 h at rt. Then 1.0 g P-trisamine was added and the reaction was shaken for 48 h. The reaction was filtered and the resin washed with CH₂Cl₂. The organic solvent was removed by rotary evaporation to yield (S)-N-[[3-[3-fluoro-4-{N-(4-methoxybenzoyl) piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a yellow glass; ¹H NMR (CDCl₃) δ 7.50 (m, 1H); 7.39 (m, 2H); 7.05 (m, 1H); 7.03 (m, 1H); 6.90 (m, 2H); 6.02 (m, 1H); 4.78 (m, 1H); 4.55 (m, 1H); 4.01 (m, 1H); 3.90 (s, 3H); 3.6-3.9 (m, 7H); 2.06 (s, 3H); and 1.95 (m, 4H).

15

Example 14

(S)-N-[[3-[3-Fluoro-4-{N-(5-cyano-2-pyridyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 14

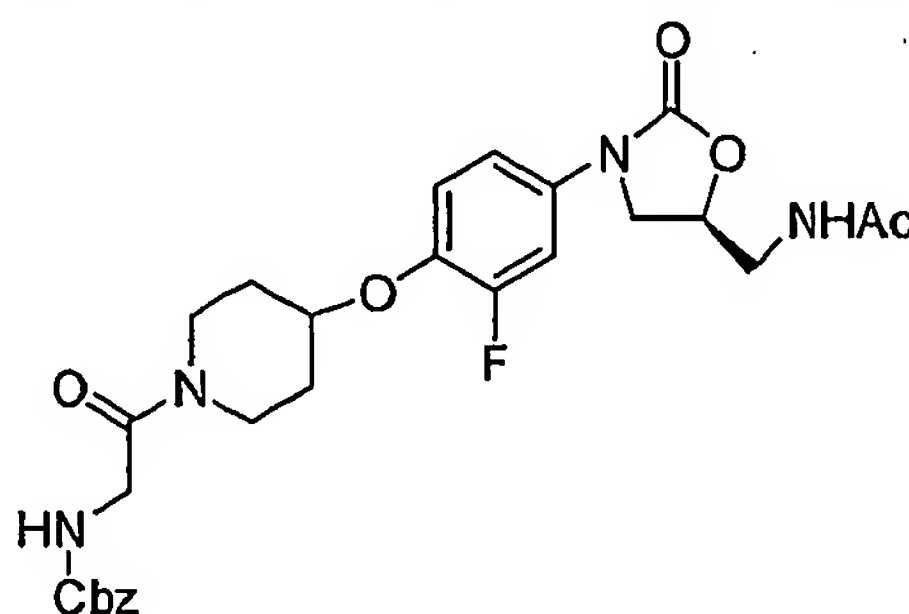
20

To a solution of 170 mg (0.48 mmol) of Compound 2 in 15 mL EtOH was added 0.15 mL NEt₃ and 80 mg (0.58 mmol) 2-chloropyridine-5-carbonitrile and the reaction was heated at 80°C for 72 h. After cooling, the reaction was poured

into 50 mL H₂O and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the crude product. Silica gel chromatography (1% MeOH in EtOAc) yielded 160 mg (73%) of (S)-N-[[3-[3-fluoro-4-{N-(5-cyano-2-pyridyl)piperidiny]4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a yellow solid; mp 78-84°C, MS (CI) [M+H]⁺ 454.

Example 15

(S)-N-[[3-[3-Fluoro-4-{N-(α-phenylmethoxycarbonylaminoacetyl)piperidiny]4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

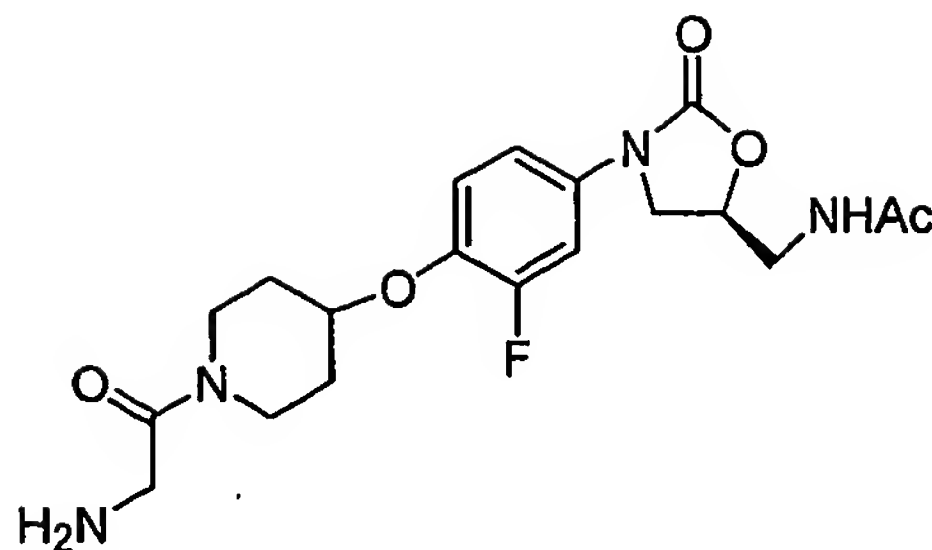


Compound 15

To a solution of 266 mg (0.76 mmol) of Compound 2 in 15 mL CH₂Cl₂ was added 0.2 mL NEt₃ and 188 mg (0.89 mmol) phenylmethoxycarbonylglycine acid fluoride and the reaction was stirred at rt for 1.5 h. Then the reaction was poured into 50 mL sat. NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and the solvent removed by rotary evaporation afford 375 mg (91%) of crude (S)-N-[[3-[3-fluoro-4-{N-(α-phenylmethoxycarbonylamino acetyl)piperidiny]4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. ¹H NMR (CDCl₃) δ 7.50 (m, 1H); 7.39 (m, 5H); 7.11 (m, 1H); 7.03 (m, 1H); 6.24 (m, 1H); 5.87 (m, 1H); 5.15 (s, 2H); 4.75 (m, 1H); 4.52 (m, 1H); 4.06 (m, 3H); 3.6-3.8 (m, 6H); 3.37 (m, 1H); 2.10 (s, 3H); and 1.90 (m, 4H).

Example 16

(S)-N-[[3-[3-Fluoro-4-{N-α-aminoacetyl)piperidiny]4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



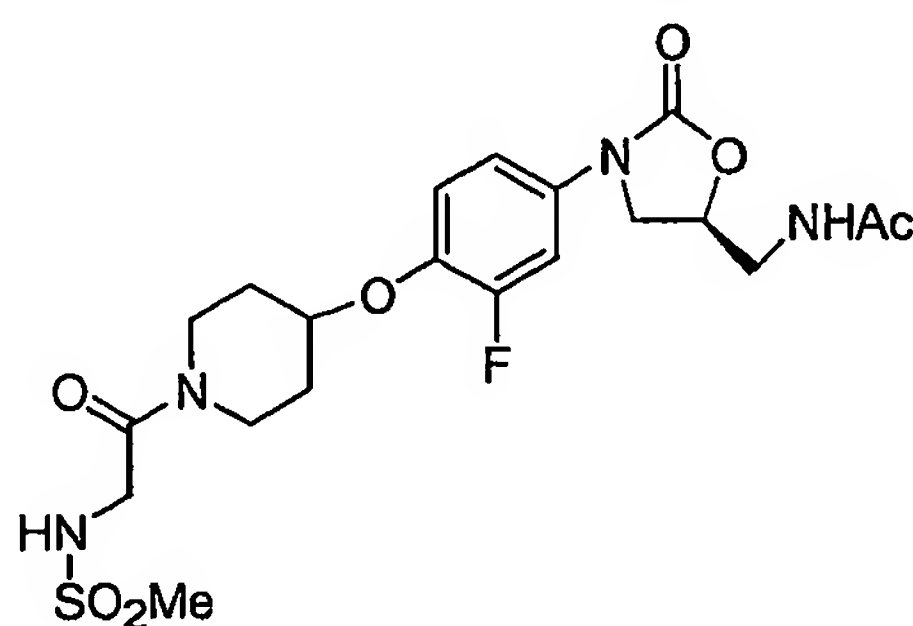
Compound 16

A solution of 340 mg (0.62 mmol) of Compound 15 in 30 mL of EtOH was
 5 treated with 36 mg 10% Pd/C, followed by hydrogenation at 50 psi overnight. The
 suspension was filtered through celite and the filtrate evaporated under reduced
 pressure to afford crude amine. Trituration of the crude solid with CHCl_3 yielded
 (S)-N-[[3-[3-fluoro-4-{N-(α -amino acetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-
 oxazolidinyl]methyl] acetamide; mp 142-146°C, MS (CI) $[\text{M}+\text{H}]^+$ 409.

10

Example 17

(S)-N-[[3-[3-Fluoro-4-{N-(α -methylsulfonylaminoacetyl)piperidinyl-4-oxy}phenyl]-
 2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 17

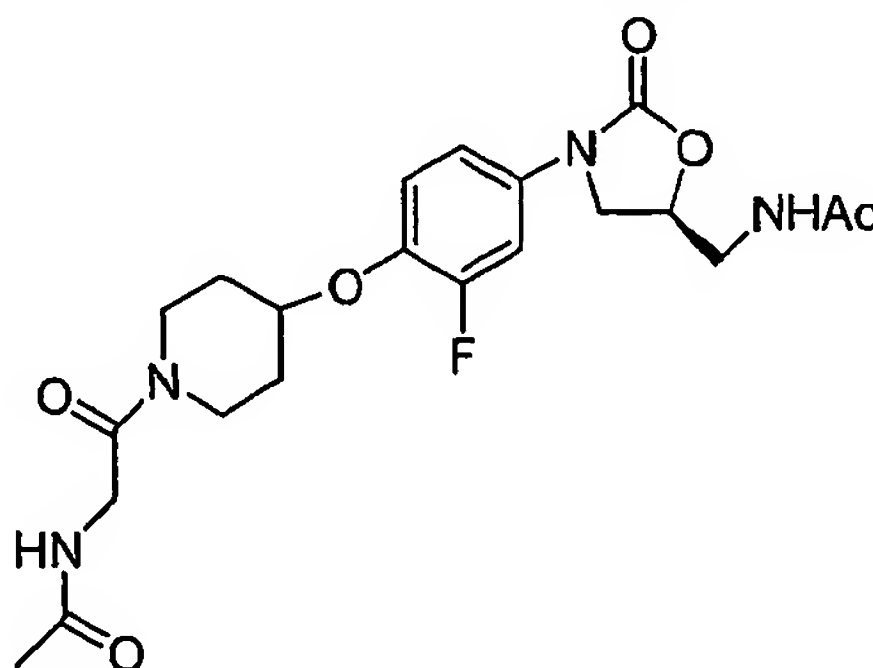
15.

To a solution of 750 mg (4.28 mmol) Boc-glycine in 25 mL CH_2Cl_2 was
 added 0.6 mL DAST and the reaction stirred at rt for 20 min. Then the reaction
 20 was washed with cold H_2O , the organic layer dried over MgSO_4 , filtered, and the
 solvent removed under reduced pressure to give a brown solid. To a solution of
 this acid fluoride in 40 mL CH_2Cl_2 was added 327 mg (0.70 mmol) of the TFA salt
 from Example 2 and 0.23 mL NEt_3 and the reaction stirred at rt for 16 h. The
 reaction was poured into 50 mL sat. NaHCO_3 , extracted with CH_2Cl_2 , washed with

H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give 388 mg of the amide as a beige foam. To a solution of 0.70 mmol of this amide was added 0.55 mL trifluoroacetic acid and the reaction stirred at rt for 20 h. The volatiles were evaporated under reduced pressure to give a brown oil. To this TFA salt in 30 mL CH₂Cl₂ was added 0.23 mL NEt₃ and 0.07 mL (0.90 mmol) methanesulfonyl chloride and the reaction stirred at rt for 18 h. The reaction was poured into 50 mL sat. NaHCO₃, extracted with CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give the crude sulfonamide. Purification by silica gel chromatography (5% MeOH in CH₂Cl₂) yielded 109 mg (32%) of (S)-N-[[3-[3-fluoro-4-{N-(α-methylsulfonylaminoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam; mp 78-82°C, MS (CI) [M+H]⁺ 487.

Example 18

(S)-N-[[3-[3-Fluoro-4-{N-(α-N-acetylaminoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



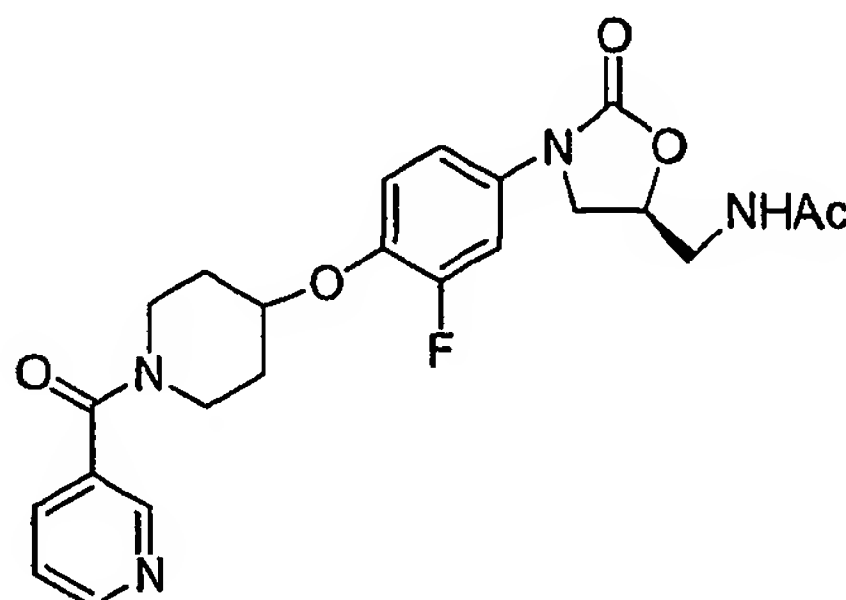
Compound 18

To a solution of 74 mg (0.63 mmol) N-acetylglycine in 10 mL CH₂Cl₂ was added 125 mg (0.65 mmol) EDCI and the reaction stirred at rt for 2 h. Then a solution of 304 mg (0.65 mmol) TFA salt from Example 2 and 0.15 mL (1.07 mmol) NEt₃ in 10 mL CH₂Cl₂ was added and the reaction stirred at rt for 3 h. The reaction was poured into 10 mL H₂O and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the crude product as a yellow oil. Silica gel chromatography (5% MeOH in CH₂Cl₂) yielded 161 mg of (S)-N-[[3-[3-fluoro-4-{N-(α-N-

acetylaminoacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide; mp 66-68°C, MS (CI) [M+H]⁺ 451.

Example 19

5 (S)-N-[[3-[3-Fluoro-4-{N-(3-pyridoyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide

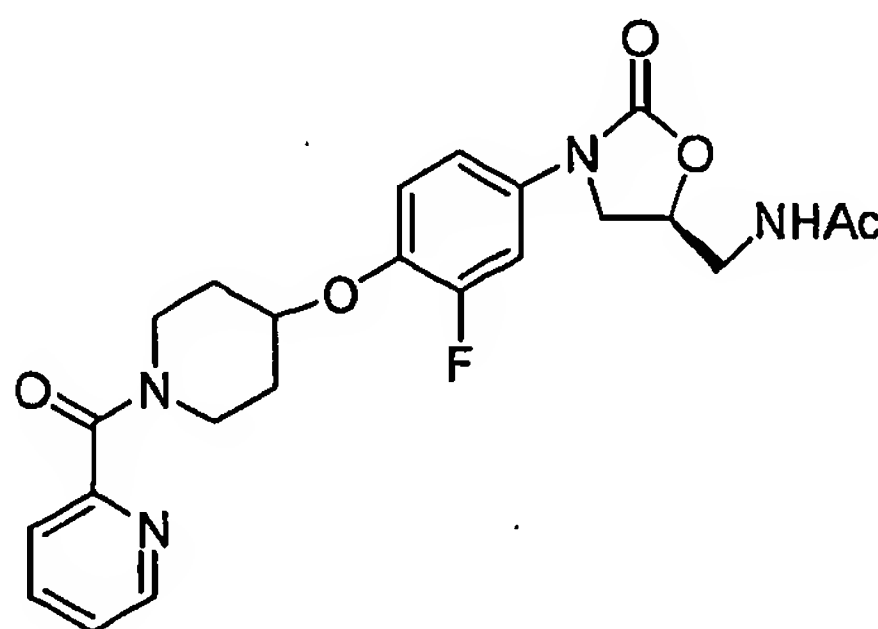


Compound 19

10 To a solution of 257 mg (0.55 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.4 mL (2.86 mmol) NEt₃ and 105 mg (0.59 mmol) nicotinoyl chloride hydrochloride and the reaction stirred at rt for 20 h. The reaction was poured into 50 mL sat. NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent
15 removed by rotary evaporation to yield 161 mg (64%) of (S)-N-[[3-[3-fluoro-4-{N-(3-pyridoyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide; mp 49-53°C, MS (CI) [M+H]⁺ 457.

Example 20

20 (S)-N-[[3-[3-Fluoro-4-{N-(2-pyridoyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide

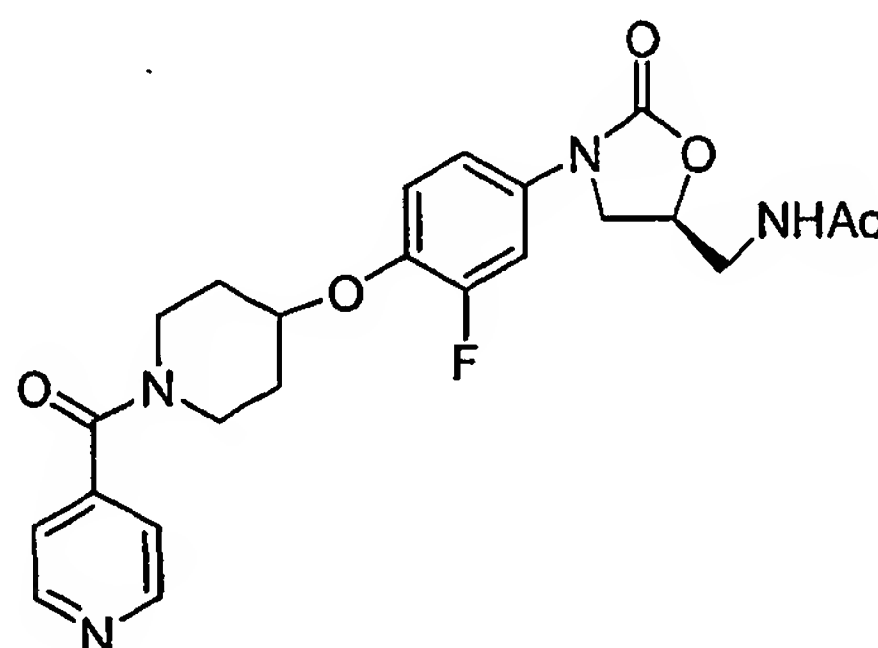


Compound 20

To a solution of 281 mg (0.60 mmol) of the TFA salt in Example 2 in 50 mL CH_2Cl_2 was added 0.3 mL NEt_3 and 110 mg (0.62 mmol) pyridine 2-carbonyl chloride hydrochloride and the reaction stirred at rt for 72 h. The reaction was poured into 50 mL sat. NaHCO_3 , and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield 190 mg (69%) of (S)-N-[[3-[3-fluoro-4-{N-(2-pyridoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 55-58°C, MS (CI) $[\text{M}+\text{H}]^+$ 457.

Example 21

(S)-N-[[3-[3-Fluoro-4-{N-(4-pyridoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



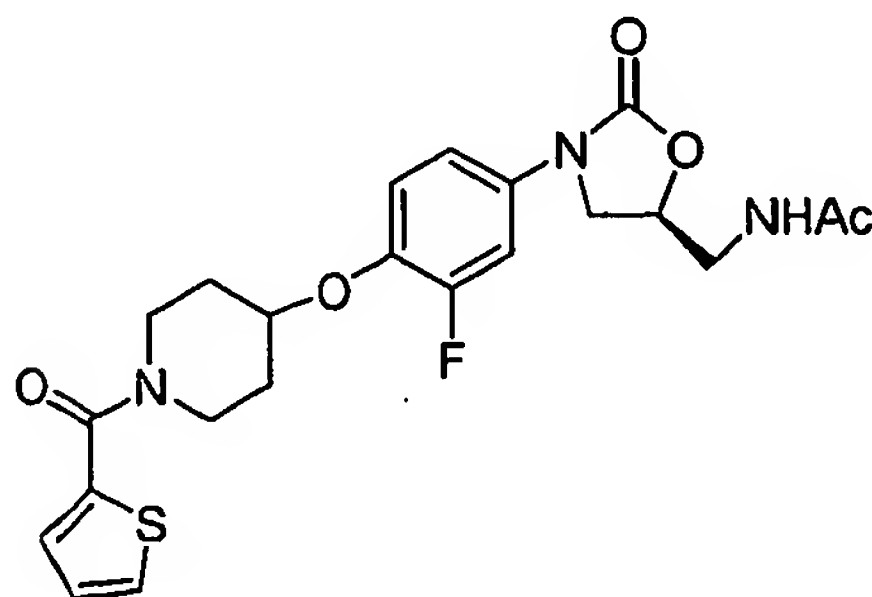
Compound 21

To a solution of 285 mg (0.61 mmol) of the TFA salt in Example 2 in 25 mL CH_2Cl_2 was added 0.5 mL NEt_3 and 123 mg (0.69 mmol) isonicotinoyl chloride hydrochloride and the reaction stirred at rt for 20 h. The reaction was poured into 50 mL sat. NaHCO_3 , and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield 29 mg (10%) of (S)-N-[[3-[3-fluoro-4-{N-(4-pyridoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam. ^1H NMR (CDCl_3) δ 8.73 (m, 2H); 7.50 (m, 1H); 7.41 (m, 2H); 7.06 (m, 2H); 6.08 (br t, 1H); 4.69 (m, 1H); 4.54 (m, 1H); 4.04 (m, 1H); 3.90 (m, 2H); 3.6-3.8 (m, 4H); 3.34 (m, 1H); 2.03 (s, 3H); 1.97 (m, 2H); and 1.82 (m, 2H).

Example 22

(S)-N-[[3-[3-Fluoro-4-{N-(2-thienylcarbonyl)piperidinyl-4-oxy}phenyl]-

2-oxo-5-oxazolidinyl]methyl]acetamide



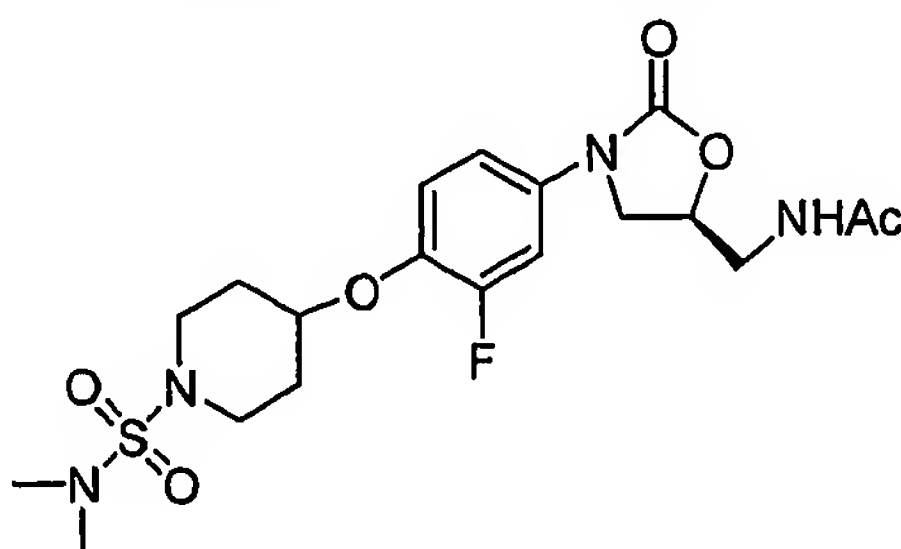
Compound 22

- 5 To a solution of 251 mg (0.55 mmol) of the TFA salt in Example 2 in 25 mL CH_2Cl_2 was added 0.2 mL NEt_3 and 0.07 mL (0.65 mmol) 2-thiophenecarbonyl chloride and the reaction stirred at rt for 72 h. The reaction was poured into 50 mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary
- 10 evaporation to give the crude product. The crude material was dissolved in 50 mL CH_2Cl_2 , P-trisamine resin added and the mixture stirred for 2 h. The reaction was filtered and the solvent evaporated under reduced pressure to give (S)-N-[[3-[3-fluoro-4-{N-(2-thienylcarbonyl)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 48-51°C, MS (CI) $[\text{M}+\text{H}]^+$ 462.

15

Example 23

(S)-N-[[3-[3-Fluoro-4-{N-(dimethylsulfamoyl)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 23

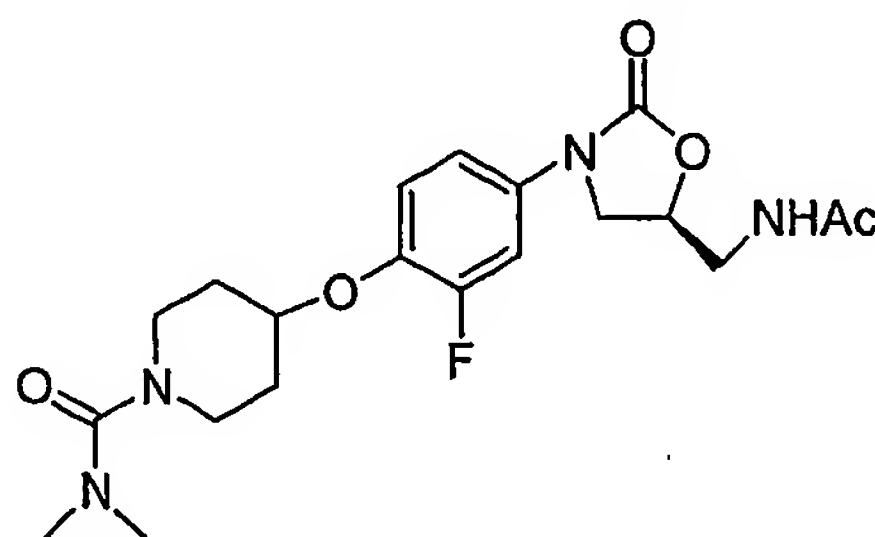
20

To a solution of 179 mg (0.38 mmol) of the TFA salt in Example 2 in 20 mL CH_2Cl_2 was added 0.12 mL NEt_3 and 0.05 mL (0.47 mmol) dimethylsulfamoyl chloride and the reaction stirred at rt for 18 h. The reaction was poured into 50

mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to give the crude product. The crude oil was crystallized from warm $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ to give (S)-N-[[3-[3-fluoro-4-{N-(dimethylsulfamoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 132-134°C, MS (CI) $[\text{M}+\text{H}]^+$ 459.

Example 24

(S)-N-[[3-[3-Fluoro-4-{N-(dimethylcarbamoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

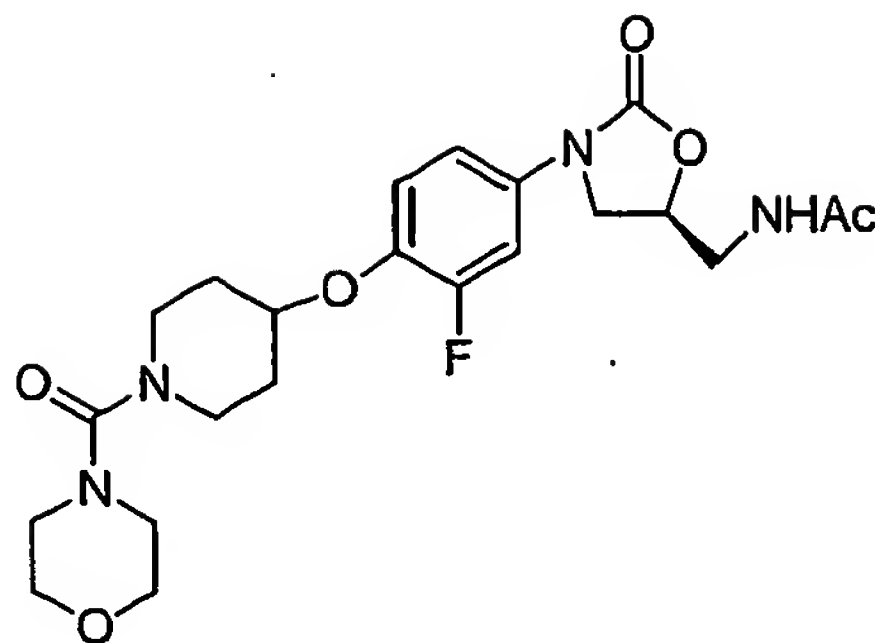


Compound 24

To a solution of 229 mg (0.49 mmol) of the TFA salt in Example 2 in 20 mL CH_2Cl_2 was added 0.15 mL (1.08 mmol) NEt_3 and 0.06 mL (0.65 mmol) dimethylcarbamoylchloride and the reaction stirred at rt overnight. The reaction was poured into 50 mL sat. NaHCO_3 , and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to give the crude product. The crude oil was crystallized from warm $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ to give 175 mg (85%) of (S)-N-[[3-[3-fluoro-4-{N-(dimethylcarbamoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 129-131°C, MS (CI) $[\text{M}+\text{H}]^+$ 423.

Example 25

(S)-N-[[3-[3-Fluoro-4-{N-(4-morpholinocarbamoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



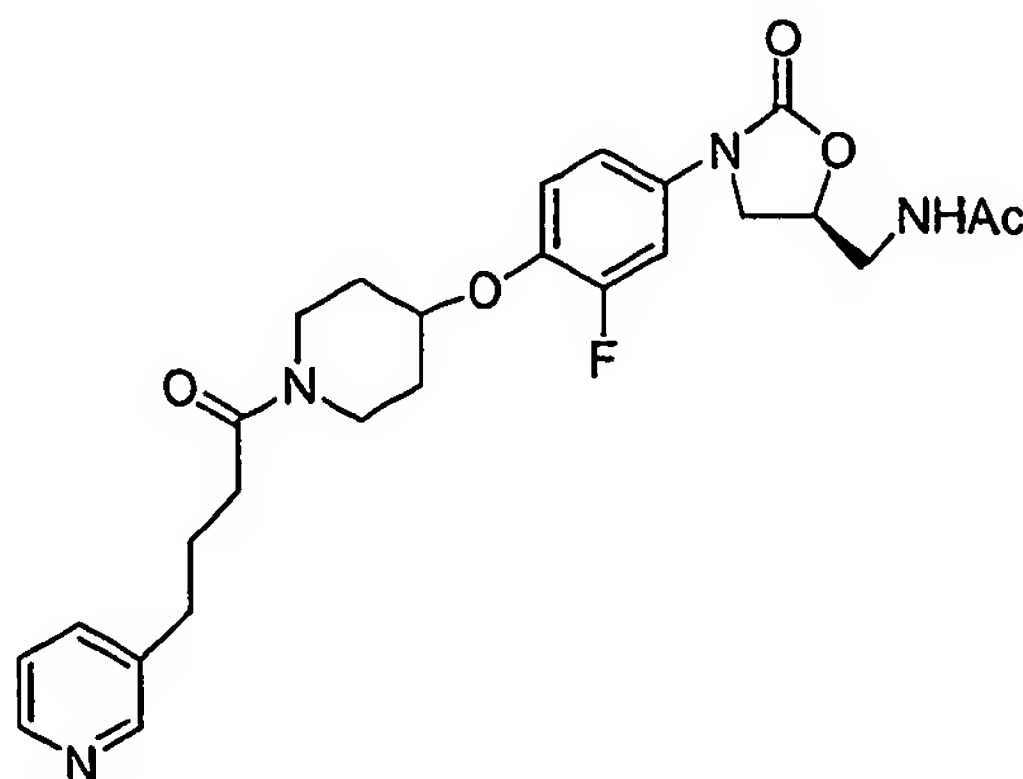
Compound 25

To a solution of 205 mg (0.44 mmol) of the TFA salt in Example 2 in 25 mL
 5 CH₂Cl₂ was added 0.13 mL NEt₃ and 0.06 mL (0.51 mmol) 4-morpholinecarbonyl
 chloride and the reaction stirred for 4 h. The reaction was poured into 50 mL sat.
 NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were washed
 with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary
 evaporation to give the crude product. The crude product was triturated with Et₂O
 10 and hexanes to give 198 mg (97%) of (S)-N-[[3-[3-fluoro-4-{N-(4-
 morpholinocarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-
 oxazolidinyl]methyl]acetamide as a white solid; mp 167-170°C, MS (CI) [M+H]⁺
 465.

15

Example 26

(S)-N-[[3-[3-Fluoro-4-{N-(4-pyridin-3-yl-butyryl)piperidinyl-4-oxy}phenyl]-
 2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 26

20

4-Pyridin-3-yl-butyronitrile:

To a solution of 0.66 mL (5.11 mmol) 3-pyridine propanol in 5 mL CH₂Cl₂ at 0°C was added 0.62 mL (7.67 mmol) pyridine and 0.47 mL (6.14 mmol) methanesulfonyl chloride and the reaction stirred for 4 h. The solution was concentrated under reduced pressure and the crude mesylate dissolved in 10 mL DMF. To this solution was added 902 mg (18.41 mmol) sodium cyanide and the reaction stirred at 60°C for 3 days. Then the solution was cooled, diluted with H₂O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, and the solvent removed under reduced pressure to give a dark red oil. The crude nitrile was purified by dissolving in EtOAc, washing with H₂O, concentrating, and filtering through a silica gel plug (5% MeOH in CH₂Cl₂) to yield 425 mg (57%) of the nitrile.

4-Pyridin-3-yl-butyric acid:

A solution of 425 mg (2.91 mmol) of 4-pyridin-3-yl-butyronitrile in 15 mL conc. HCl was refluxed for 8 h. The volatiles were evaporated under reduced pressure and the residue dissolved in EtOH. Upon addition of acetone and cooling a dark brown solid precipitated. The filtrate was concentrated and triturated with cold acetone to collect a total of 334 mg (69%) of the carboxylic acid.

4-Pyridin-3-yl-butyryl chloride:

To a solution of 247 mg (1.49 mmol) of 4-pyridin-3-yl-butyric acid in 10 mL CH₂Cl₂ was added one drop DMF and 2.3 mL (4.56 mmol) oxalyl chloride and the mixture stirred at rt for 4 h. The volatiles were evaporated under reduced pressure and the material used crude in the following procedure.

(S)-N-[[3-[3-fluoro-4-{N-(4-pyridin-3-yl-butyryl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 26):

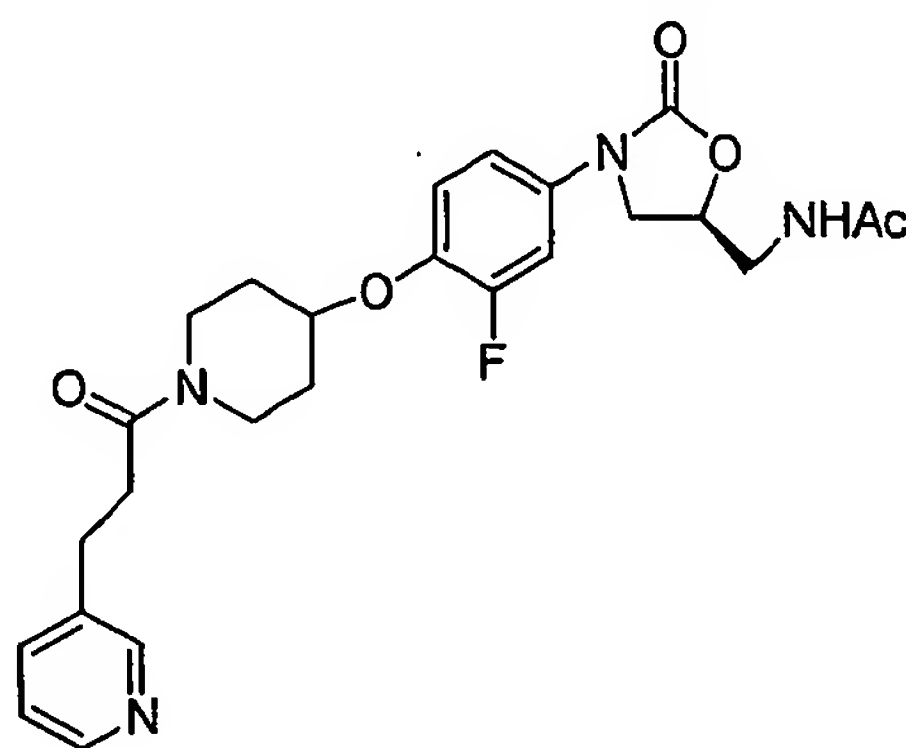
To a solution of 597 mg (1.29 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.54 mL (3.86 mmol) NEt₃ at 0°C and the reaction stirred for 30 min, warming to rt. Then the solution was cooled to 0°C, a solution of the previous acid chloride in 20 mL CH₂Cl₂ was added, and the reaction allowed to warm to rt. The reaction was diluted with CH₂Cl₂, washed with sat. NaHCO₃ (2 x

30 mL), washed with H₂O (2 x 30 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a tan foam.

Purification by silica gel chromatography (10% MeOH in EtOAc) yielded 152 mg (24%) of (S)-N-[[3-[3-fluoro-4-{N-(4-pyridin-3-yl-butyryl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as an off-white foam; mp 42-45°C, MS (CI) [M+H]⁺ 499.

Example 27

(S)-N-[[3-[3-Fluoro-4-{N-(3-pyridin-3-yl-propionyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 27

3-Pyridine propionyl chloride:

To a solution of 300 mg (1.99 mmol) 3-pyridine propionic acid in 10 mL CH₂Cl₂ was added one drop DMF and 2.3 mL (4.56 mmol) oxalyl chloride, and the mixture stirred at rt for 4 h. The volatiles were evaporated under reduced pressure and the material used crude in the following procedure.

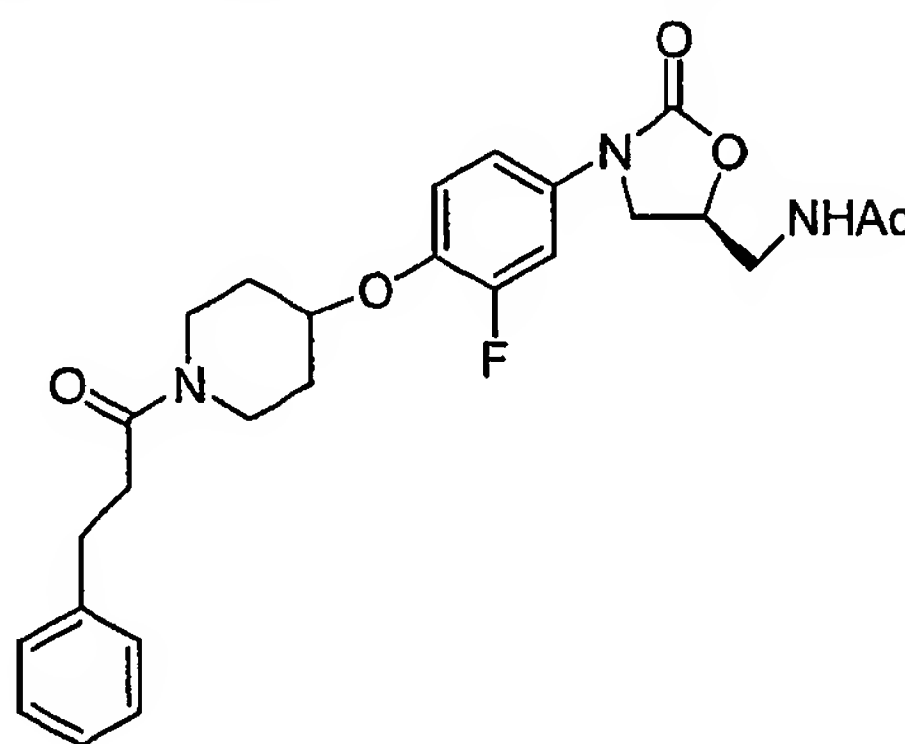
(S)-N-[[3-[3-fluoro-4-{N-(3-pyridin-3-yl-propionyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 27):

To a solution of 917 mg (1.97 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.75 mL (5.41 mmol) NEt₃ at 0°C and the reaction stirred for 30 min, warming to rt. Then the solution was cooled to 0°C, a solution of the previous acid chloride in 20 mL CH₂Cl₂ was added along with an additional equivalent of NEt₃, and the reaction allowed to warm to rt and stirred overnight. The reaction was diluted with CH₂Cl₂, washed with sat. NaHCO₃ (2 x 30 mL),

washed with H₂O (2 x 30 mL), dried over Na₂SO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a dark orange oil. Purification by silica gel chromatography (10% MeOH and 1% NEt₃ in EtOAc) yielded 110 mg of (S)-N-[[3-[3-fluoro-4-{N-(3-pyridin-3-yl-propionyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a foam; mp 45-47°C, MS (CI) [M+H]⁺ 485.

Example 28

(S)-N-[[3-[3-Fluoro-4-{N-(3-phenyl-propionyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

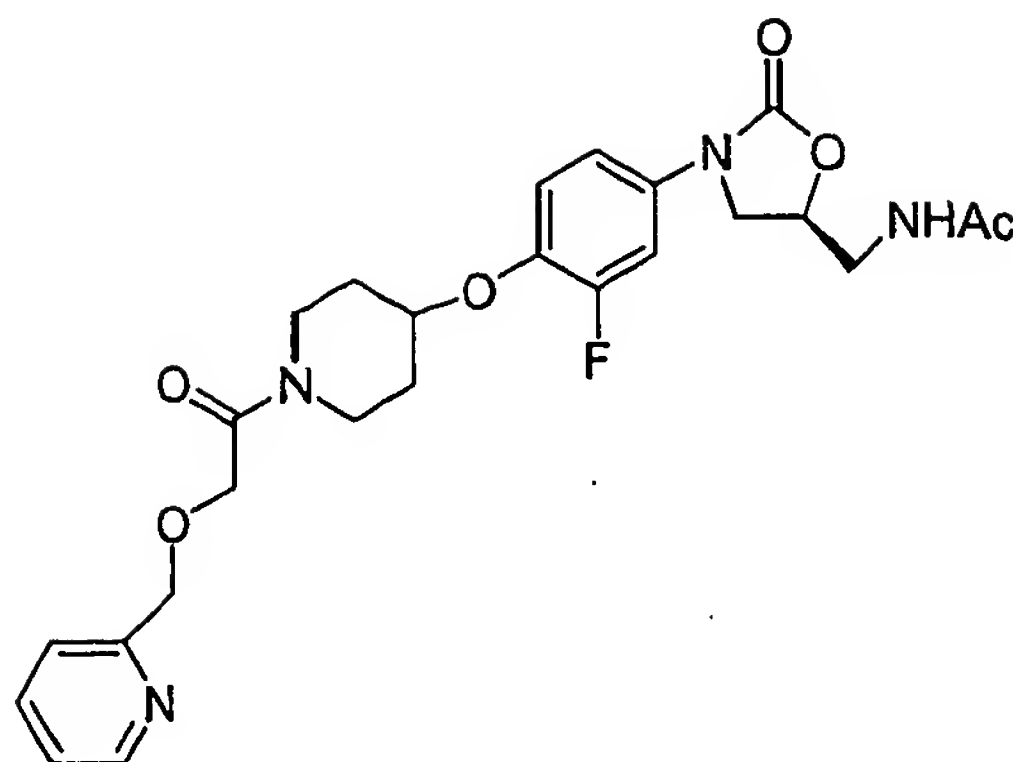


Compound 28

To a solution of 133 mg (0.27 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.07 mL (0.53 mmol) NEt₃ and 0.04 mL (0.29 mmol) hydrocinnamoyl chloride, and the reaction allowed to warm to rt and stirred for 1 h. The reaction was diluted with CH₂Cl₂, washed with sat. NaHCO₃ (2 x 30 mL), washed with H₂O (2 x 30 mL), dried over Na₂SO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a colorless oil. Purification by silica gel chromatography (10% MeOH in EtOAc) yielded a transparent glass. This material was triturated with EtOAc and hexanes to give (S)-N-[[3-[3-fluoro-4-{N-(3-phenyl-propionyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; MS (CI) [M+H]⁺ 484.

Example 29

(S)-N-[[3-[4-{N-(Pyridin-2-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 29

(Pyridin-2-yl-methoxy)-acetic acid *t*-butyl ester:

- 5 To a solution of 0.5 mL (5.18 mmol) 2-pyridylmethanol in 20 mL THF at 0°C was added 270 mg (6.75 mmol) NaH and the reaction stirred for 0.25 h. Then 0.82 mL *t*-butylbromoacetate was added and the reaction warmed to rt and stirred for 12 days. The reaction was poured into 100 mL H₂O, extracted with CH₂Cl₂ (2 x 100 mL), the combined organic layers washed with brine, dried over MgSO₄,
 10 filtered, and the solvent removed under reduced pressure to give 1.16 g (61%) as a brown oil.

(Pyridin-2-yl-methoxy)-acetic acid:

- To a solution of 706 mg (3.16 mmol) of (pyridin-3-yl-methoxy)-acetic acid *t*-
 15 butyl ester and 1.5 mL of TFA in 25 mL of methylene chloride were stirred at room temperature for 20 hr. The volatiles were evaporated to afford crude acid.

(S)-N-[[3-[4-{N-(Pyridin-2-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 29):

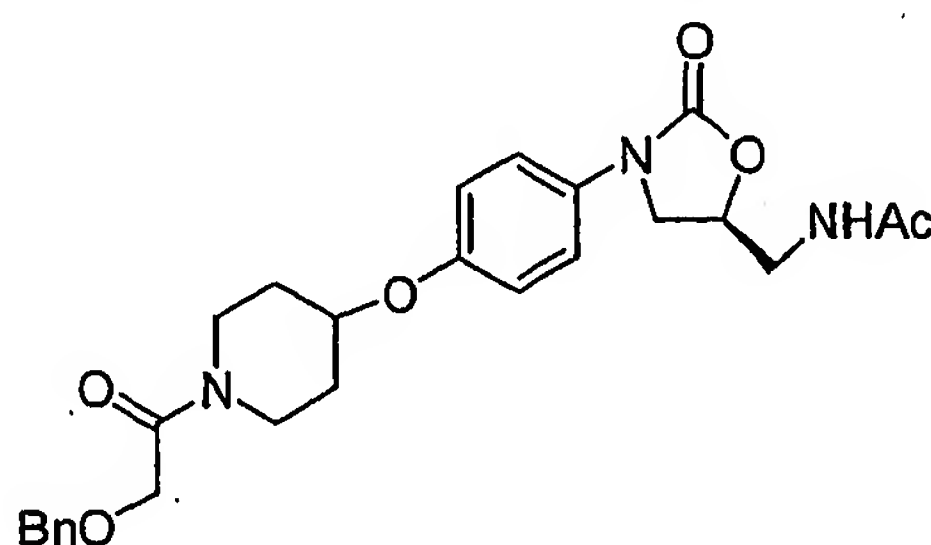
- 20 To 460 mg (1.63 mmol) of (pyridin-2-yl-methoxy)acetic acid in 100 mL CH₂Cl₂ was added 405 mg (2.11 mmol) EDCI, 634 mg (1.36 mmol) of the TFA salt from example 1, and 4.5 mL (32.2 mmol) NEt₃. The reaction was stirred at rt for 5 days. Then the mixture was poured into 125 mL H₂O, extracted with CH₂Cl₂, the organic layers washed with brine, dried over MgSO₄, filtered, and the solvent
 25 removed by rotary evaporation. Purification by silica gel chromatography (5% MeOH in CH₂Cl₂) yielded 403 mg (59%) of (S)-N-[[3-[4-{N-(pyridin-2-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

as a yellow semi-solid. ^1H NMR (CDCl_3) δ 8.54 (m, 1H); 7.72 (m, 1H); 7.49 (m, 2H); 7.23 (m, 1H); 7.09 (m, 1H); 7.00 (m, 1H); 6.10 (m, 1H); 4.78 (m, 1H); 4.71 (s, 2H); 4.48 (m, 1H); 4.32 (s, 2H); 4.04 (m, 1H); 3.6-3.8 (m, 6H); 3.45 (m, 1H); 2.03 (s, 3H); and 1.83 (m, 4H).

5

Example 30

(S)-N-[[[3-[4-{N-(Benzyloxyacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 30

10

1-[N-(*t*-Butoxycarbonyl)piperidiny-4-oxy]-4-nitrobenzene:

To a solution of 10.0 g (49.68 mmol) of N-(*t*-butoxycarbonyl)-4-piperidinol from example 1 in 125 mL dry THF at 0°C was added dropwise 74 mL (74.53 mmol) 1M KO^tBu. After stirring at 0°C for 0.5 h, 5.27 mL (49.68 mmol) *p*-fluoronitrobenzene was added and the reaction warmed to rt and stirred overnight. The volatiles were removed under reduced pressure and the reaction diluted with 800 mL H₂O. The mixture was extracted with CH₂Cl₂ (2 x 500 mL) and a brown solid removed by filtration. The combined aqueous layers were washed with H₂O, dried with MgSO₄, filtered, and the solvent removed by rotary evaporation to give an orange solid. Purification by silica gel chromatography (3:1 hexane:EtOAc) yielded 6.98 g (44%) of 1-[N-(*t*-butoxycarbonyl)piperidiny-4-oxy]-4-nitrobenzene as a pale yellow solid. An additional 3.20 g of product was extracted from the brown solid; MS (CI) [M+Na]⁺ 345.

25

1-[4-(N-*t*-Butoxycarbonyl)piperidiny-4-oxy]-4-aminobenzene:

To 6.97 g (21.62 mmol) of 1-[N-(*t*-butoxycarbonyl)piperidiny-4-oxy]-4-nitrobenzene in 250 mL MeOH was added 6.81 g (108.1 mmol) ammonium formate and a catalytic amount of 10% Pd/C, and the reaction heated at 50°C

under N₂ for 5 h. The reaction was filtered through a pad of celite and the filtrate evaporated to afford crude aniline as an orange oil. The material was used without further purification in the next step.

5 1-{N-(*t*-Butoxycarbonyl)piperidiny-4-oxy}-4-(phenylmethoxycarbonylamino)benzene:

To 6.32 g (21.62 mmol) of 1-[4-(*N*-*t*-butoxycarbonyl)piperidiny-4-oxy]-4-aminobenzene in 300 mL 2:1 acetone:H₂O at 0°C was added 4.50 g (52.97 mmol) NaHCO₃ and 3.30 mL (23.13 mmol) benzylchloroformate. The reaction was
10 allowed to warm to rt and stirred overnight. Then the volatiles were evaporated, the residue diluted with 200 mL H₂O and extracted with Et₂O (2 x 200 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give 8.62 g (93%) of 4-{N-(*t*-
butoxycarbonyl)piperidiny-4-oxy}-1-(phenylmethoxycarbonylamino)benzene as a
15 pink solid; mp 107-108°C, MS (CI) [M+Na]⁺ 449.

(R)-[3-[4-{N-(*t*-Butoxycarbonyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidiny]methanol:

To 8.23 g (19.31 mmol) of 4-{N-(*t*-butoxycarbonyl)piperidiny-4-oxy}-1-(phenylmethoxycarbonylamino)benzene in 300 mL dry THF at -78°C was added
20 10.8 mL (27.03 mmol) 2.5M *n*-BuLi and the reaction stirred for 1 h. Then 3.84 mL (27.03 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred for 3 days. Then an additional 2 mL 2.5M *n*-BuLi was added and the reaction stirred for another day. The reaction was carefully poured
25 into 150 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (EtOAc) gave 4.34 g (57%) of (R)-[3-[4-{N-(*t*-butoxycarbonyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidiny]methanol as a yellow solid; mp 110-112°C, MS (CI) [M+Na]⁺
30 415.

(R)-[3-[4-{N-(*t*-Butoxycarbonyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidiny]methyl methanesulfonate:

To 4.23 g (10.79 mmol) of (R)-[3-[4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol in 75 mL CH₂Cl₂ at 0°C was added 3.0 mL (21.58 mmol) NEt₃ and 1.2 mL (15.11 mmol) methanesulfonyl chloride. The reaction was allowed to warm to rt over an hour and washed with H₂O (2 x 50 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 5.0 g (99%) of (S)-[3-[4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate as a white foam.

(R)-[3-[4-{N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of 5.0 g (10.63 mmol) of (R)-[3-[4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate in 100 mL DMF was added 2.63 g (40.38 mmol) sodium azide and the reaction was heated at 70°C overnight. Then the reaction was poured into 200 mL H₂O and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with H₂O (2 x 150 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 4.4 g (99%) of (R)-[3-[4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide as a yellow oil; MS (CI) [M+Na]⁺ 440.

(S)-N-[[3-[4-{N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A solution of 4.48 g (10.73 mmol) of (R)-[3-[4-{N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL of EtOAc was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi for 20 h. To this mixture at 0°C was added 1.1 mL (12.88 mmol) pyridine and 3.2 mL (34.34 mmol) acetic anhydride. The reaction was stirred for 30 min at 0°C, then warmed to rt over 1 h. The reaction was filtered through celite, eluting with EtOAc. The volatiles were removed under reduced pressure and the yellow solid dissolved in EtOAc and washed with H₂O (3 x 100 mL). A white solid was removed via filtration. The organic layers were concentrated to an orange oil and triturated using EtOAc and hexanes to yield a white solid. The white solids were combined to yield 1.48 g (31%) of (S)-N-[[3-[4-{N-(*t*-butoxycarbonyl)piperidinyl-4-

oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide; mp 185-186°C, MS (CI) [M+Na]⁺ 456.

(S)-N-[[3-[4-{Piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide:

5 To a solution of 1.48 g (3.41 mmol) of the previous Boc-carbamate ((S)-N-[[3-[4-{ N-(*t*-butoxycarbonyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide) in 225 mL CH₂Cl₂ was added 2.6 mL (34.14 mmol) trifluoroacetic acid and the reaction stirred at rt for 2 h. The reaction was diluted with 50 mL CH₂Cl₂, washed with NaHCO₃ (2 x 100 mL), dried over MgSO₄,
10 filtered, and evaporated under reduced pressure to yield 980 mg (86%) of (S)-N-[[3-[4-{piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide as a yellow oil.

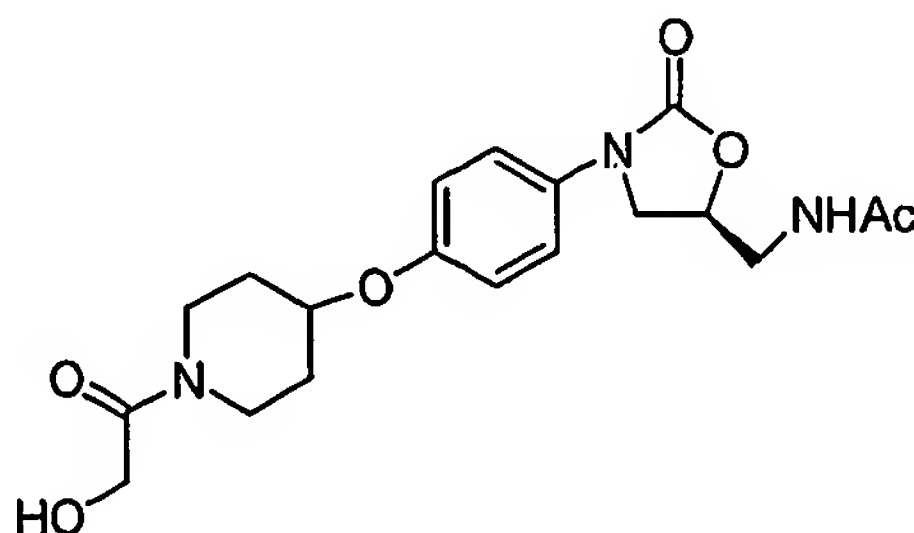
(S)-N-[[3-[4-{N-(Benzyloxyacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide:

15 To a suspension of 160 mg (0.48 mmol) of (S)-N-[[3-[4-{piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide in 20 mL CH₂Cl₂ was added 0.13 mL (0.96 mmol) NEt₃ and 0.08 ml (0.53 mmol) benzyloxyacetyl chloride. After stirring for 2 h, the reaction was poured into 75 mL H₂O and extracted with
20 CH₂Cl₂ (4 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure. Silica gel chromatography (10% MeOH in EtOAc) afforded (S)-N-[[3-[4-{N-(benzyloxyacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl] acetamide as a white foam; mp 53-55°C, MS (CI) [M+H]⁺ 482.

25

Example 31

(S)-N-[[3-[4-{N-(α -Hydroxyacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide

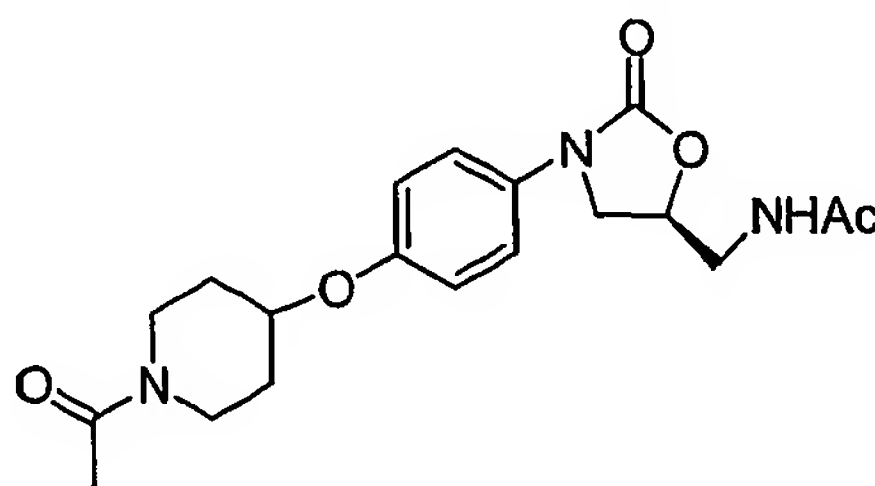


Compound 31

To a solution of 103 mg (0.21 mmol) of Compound 30 in 10 mL MeOH was added 67 mg (1.07 mmol) ammonium formate and a catalytic amount of 10% Pd/C, and the reaction was heated at 50°C for 3 days. Then the reaction was filtered through a pad of celite, eluted with EtOAc and MeOH, and the solvent removed under reduced pressure to yield 56 mg (66%) of (S)-N-[[3-[4-{N-(α -hydroxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide as a white foam; MS (CI) [M+H]⁺ 392.

Example 32

(S)-N-[[3-[4-{N-(Acetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

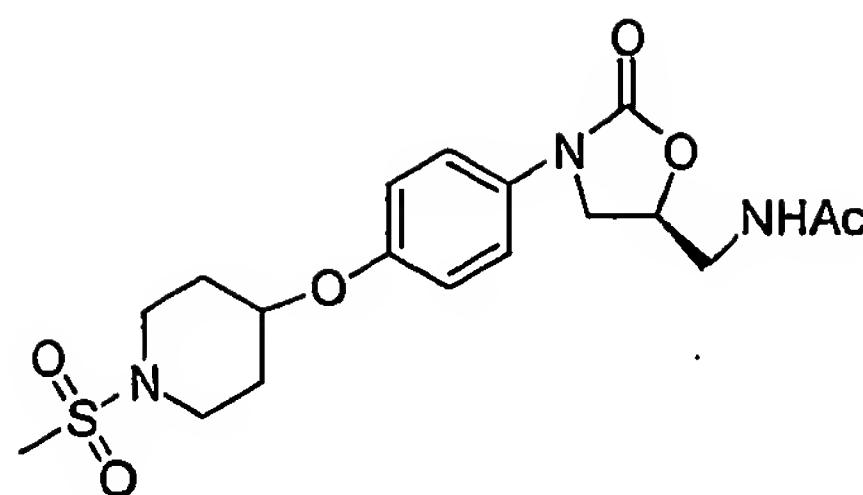


Compound 32

To a solution of 240 mg (0.72 mmol) of (S)-N-[[3-[4-{piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 20 mL CH₂Cl₂ was added 0.45 mL (3.24 mmol) NEt₃ and 0.08 mL (1.08 mmol) acetyl chloride and the reaction stirred overnight. The reaction was diluted with 50 mL CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a gold oil. Purification by silica gel chromatography (10% MeOH in EtOAc) yielded 130 mg (50%) of (S)-N-[[3-[4-{N-(acetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a colorless oil; MS (CI) [M+Na]⁺ 398.

Example 33

(S)-N-[[3-[4-{N-(Methanesulfonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

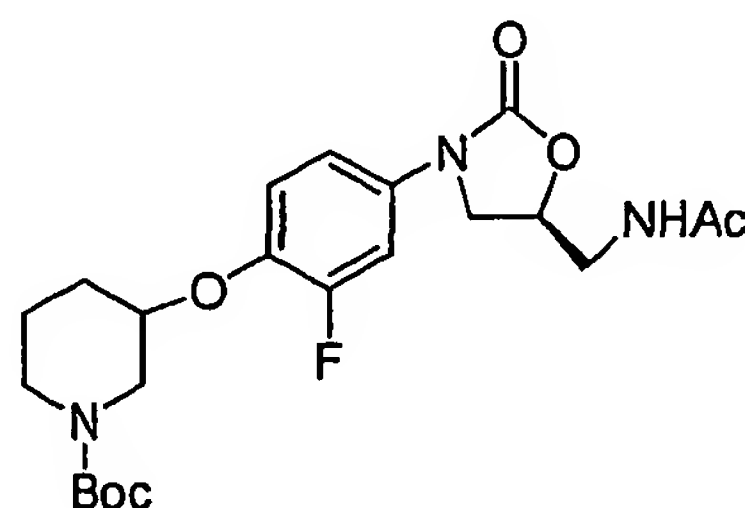


Compound 33

To a solution of 50 mg (0.15 mmol) of (S)-N-[[3-[4-{piperidin-4-
 5 oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 20 mL CH₂Cl₂ was added
 0.04 mL (0.30 mmol) NEt₃ and 0.02 mL (0.21 mmol) methanesulfonyl chloride and
 the reaction stirred overnight. The reaction was diluted with 10 mL CH₂Cl₂,
 washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary
 evaporation to give the crude product as a gold oil. Purification by silica gel
 10 chromatography (10% MeOH in EtOAc) yielded 40 mg (64%) of (S)-N-[[3-[4-{N-
 (methanesulfonyl)piperidin-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide
 as a white solid; MS (CI) [M+Na]⁺ 434.

Example 34

15 (S)-N-[[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidin-3-oxy}phenyl]-
 2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 34

20 N-(*t*-Butoxycarbonyl)-3-piperidinol:

A solution of 10.0 g (72.67 mmol) 3-hydroxypiperidine in 100 mL dry THF
 at 0°C was added 10.1 mL (72.67 mmol) NEt₃ and 15.86 g (72.67 mmol) di-*t*-
 butylcarbonate in 100 mL THF and the reaction allowed to warm to rt and stirred
 overnight. The solvent was removed under reduced pressure, the resulting
 25 residue dissolved in 300 mL CH₂Cl₂ and the solution extracted with H₂O (2 x 200

mL), dried over MgSO_4 , filtered and rotary evaporated to yield 12.66 g (87%) of N-(*t*-butoxycarbonyl)-3-piperidinol as an oil which slowly solidified to a white solid.

1-[N-(*t*-Butoxycarbonyl)piperidiny-3-yl]-2-fluoro-4-nitrobenzene:

5 To a solution of 5.0 g (24.84 mmol) of N-(*t*-butoxycarbonyl)-3-piperidinol in 75 mL dry THF at 0°C was added dropwise 37 mL (37.26 mmol) 1M KO^tBu. After stirring at 0°C for 0.5 h, 2.8 mL (24.84 mmol) 3,4-difluoronitrobenzene was added and the reaction warmed to rt and stirred for 0.5 h. The volatiles were removed under reduced pressure and the residue was dissolved in 400 mL H_2O and
10 extracted with CH_2Cl_2 (2 x 300 mL). The combined aqueous layers were dried with MgSO_4 , filtered, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (3:1 hexanes:EtOAc) yielded 5.94 g (70%) of 1-[N-(*t*-butoxycarbonyl)piperidiny-3-yl]-2-fluoro-4-nitrobenzene; MS (CI) $[\text{M}+\text{Na}]^+$ 363.

15 1-[4-(N-*t*-Butoxycarbonyl)piperidiny-3-yl]-2-fluoro-4-aminobenzene:

To 5.94 g (17.40 mmol) of 1-[N-(*t*-butoxycarbonyl)piperidiny-3-yl]-2-fluoro-4-nitrobenzene in 200 mL MeOH was added 5.49 g (87.02 mmol) ammonium formate and a catalytic amount of 10% Pd/C, and the reaction heated at 50°C under N_2 overnight. The reaction was filtered through a pad of celite and
20 the filtrate evaporated to afford crude aniline as an orange oil. The product was dissolved in 150 mL EtOAc and washed with H_2O (2 x 100), dried over MgSO_4 , filtered, and the solvent removed under reduced pressure to give 4.98 g (92%) as a light yellow oil. The material was used without further purification in the next step.

25

2-Fluoro-1-[N-(*t*-butoxycarbonyl)piperidiny-3-yl]-4-(phenylmethoxycarbonylamino)benzene:

To 4.98 g (16.08 mmol) of 1-[4-(N-*t*-butoxycarbonyl)piperidiny-3-yl]-2-fluoro-4-aminobenzene in 300 mL 2:1 acetone: H_2O at 0°C was added 3.31 g
30 (39.40 mmol) NaHCO_3 and 2.46 mL (17.20 mmol) benzylchloroformate. After stirring at rt overnight the volatiles were evaporated, the residue diluted with 200 mL H_2O and extracted with Et_2O (3 x 150 mL). The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary

evaporation. Silica gel chromatography (2:3 EtOAc:Hexanes) afforded 5.30 g (75%) of 3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}-1-(phenylmethoxycarbonylamino)benzene as a white solid; mp 109-110°C, MS (CI) [M+Na]⁺ 467.

5

(R)-[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol:

To 3.27 g (7.36 mmol) of 2-fluoro-1-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}-4-(phenylmethoxycarbonylamino)benzene in 150 mL dry THF at -78°C was added 4.1 mL (10.31 mmol) 2.5M *n*-BuLi and the reaction stirred for 1 h. Then 1.5 mL (10.31 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred overnight. The reaction was carefully poured into 100 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (EtOAc) gave 2.99 g (98%) of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol as a white foam; mp 48-50°C.

20

(R)-[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

To 1.32 g (3.22 mmol) of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol in 50 mL CH₂Cl₂ at 0°C was added 0.90 mL (6.44 mmol) NEt₃ and 0.35 mL (4.51 mmol) methanesulfonyl chloride. The reaction was allowed to warm to rt over 1 h and then washed with H₂O (2 x 30 mL), dried over MgSO₄, filtered and the solvent removed by rotary evaporation to yield 1.50 g (95%) of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate as a yellow foam.

30

(R)-[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of 1.50 g (3.07 mmol) of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl

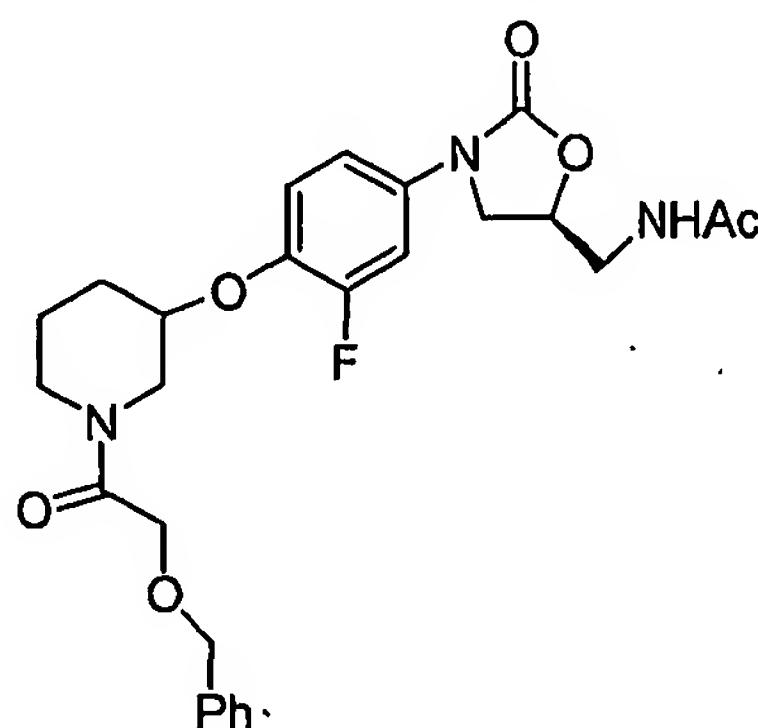
methanesulfonate in 60 mL DMF was added 758 mg (11.66 mmol) sodium azide and the reaction heated at 75°C overnight. Then the reaction was poured into 100 mL H₂O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (3 x 200 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide as a foam.

(S)-N-[[3-[3-Fluoro-4-{ N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A solution of 1.34 g (3.07 mmol) of (R)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL of EtOAc was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi for 20 h. To this mixture at 0°C was added 0.3 mL (3.68 mmol) pyridine and 0.93 mL (9.82 mmol) acetic anhydride. The reaction was stirred for 30 min at 0°C, then warmed to rt over 1 h. The reaction was filtered through celite, eluting with EtOAc. The volatiles were removed under reduced pressure. Silica gel chromatography (10% MeOH in EtOAc) yielded (S)-N-[[3-[4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy} phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 60-63°C, MS (CI) [M+Na]⁺ 474.

Example 35

(S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 35

(S)-N-[[3-[3-Fluoro-4-{piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

To a solution of 589 mg (1.31 mmol) of Compound 34 in 13 mL CH₂Cl₂ was added 1.0 mL (13.1 mmol) trifluoroacetic acid and the reaction stirred at rt for 2 h.

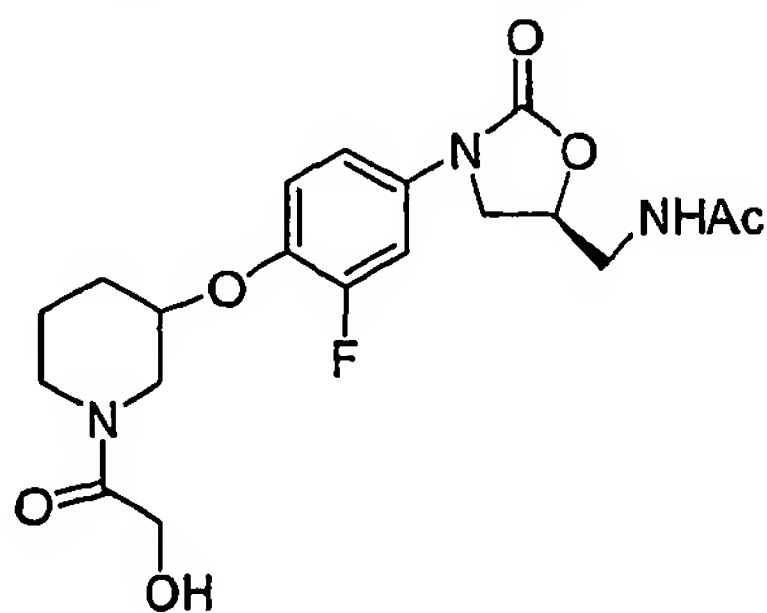
5 The volatiles were evaporated under reduced pressure to yield (S)-N-[[3-[3-fluoro-4-{piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

(S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

10 To a suspension of 303 mg (0.65 mmol) of (S)-N-[[3-[3-fluoro-4-{piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 50 mL CH₂Cl₂ was added 0.27 mL (1.96 mmol) NEt₃ and 0.11 mL (0.72 mmol) benzyloxyacetyl chloride. After stirring for 1 h, the reaction was poured into 75 mL H₂O and extracted with CH₂Cl₂ (4 x 50 mL). The combined organic layers were dried over MgSO₄,
15 filtered, and evaporated under reduced pressure to yield (S)-N-[[3-[3-fluoro-4-{N-(benzyloxyacetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide as a foam; MS (CI) [M+H]⁺ 500.

Example 36

20 (S)-N-[[3-[3-Fluoro-4-{N-(α-hydroxyacetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



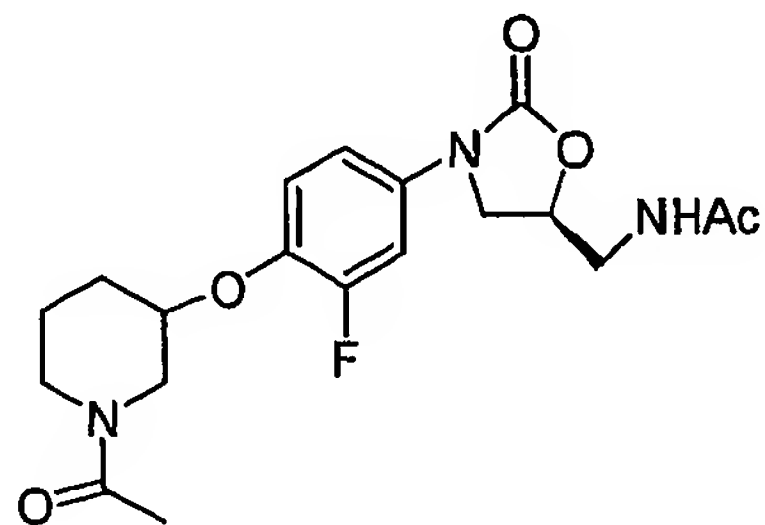
Compound 36

25 To a solution of 301 mg (0.60 mmol) of Compound 35 in 10 mL MeOH was added 190 mg ammonium formate and a catalytic amount of 10% Pd/C and the reaction was heated at reflux overnight. Then the reaction was filtered through a pad of celite and the solvent removed under reduced pressure. Silica gel chromatography (10% MeOH in EtOAc) afforded 231 mg (82%) of (S)-N-[[3-[3-

fluoro-4-{N-(α -hydroxyacetyl)piperidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinylmethyl]acetamide as a yellow foam; MS (CI) $[M+H]^+$ 410.

Example 37

5 (S)-N-[[3-[3-Fluoro-4-{N-(acetyl)piperidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinylmethyl]acetamide



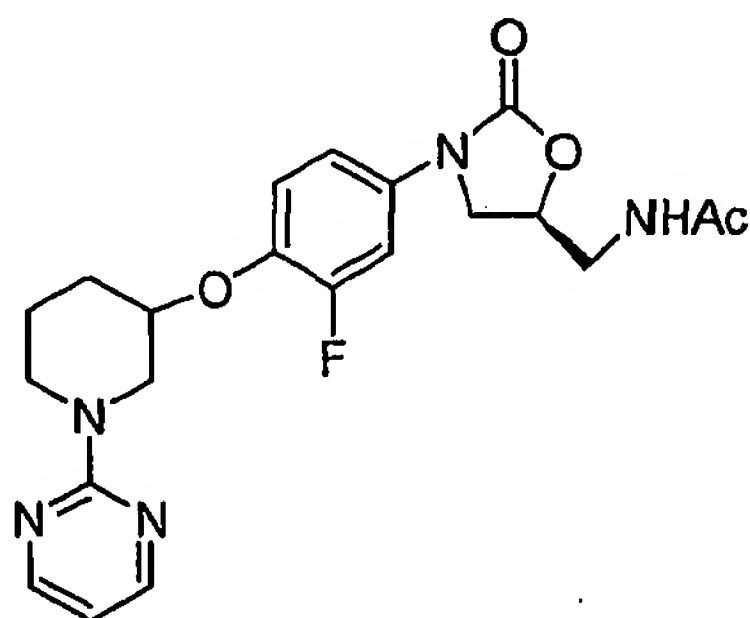
Compound 37

10 To a solution of 100 mg (0.28 mmol) of (S)-N-[[3-[3-fluoro-4-{piperidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinylmethyl]acetamide in 10 mL CH_2Cl_2 was added 0.12 mL (0.85 mmol) NEt_3 and 0.03 mL (0.43 mmol) acetyl chloride. The reaction stirred at rt for 2 h diluted with CH_2Cl_2 , washed with H_2O (2 x 100 mL), dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield the impure
15 amide. Purification by silica gel chromatography (10% MeOH in EtOAc) and trituration of the resultant oil with EtOAc and hexanes yielded (S)-N-[[3-[3-fluoro-4-{N-(acetyl)piperidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinylmethyl]acetamide as a solid.

20

Example 38

(S)-N-[[3-[3-Fluoro-4-{N-(2-pyrimidinyl)piperidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinylmethyl]acetamide

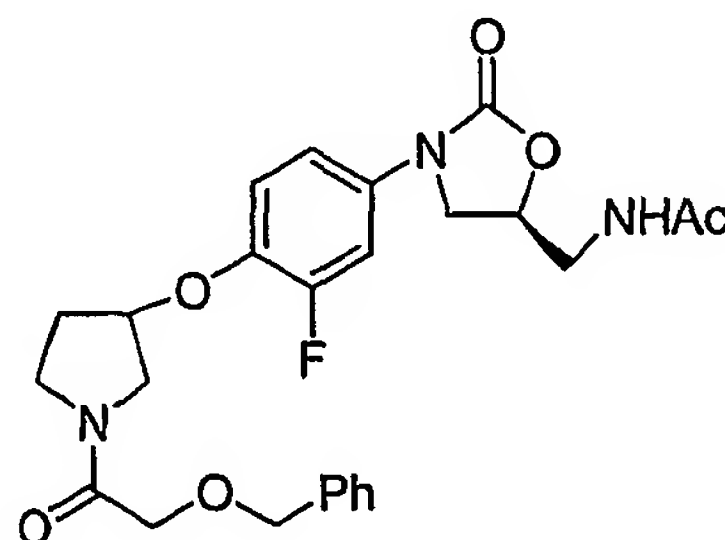


Compound 38

To a solution of 151 mg (0.33 mmol) of (S)-N-[[3-[3-fluoro-4-{piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 4 mL EtOH was added 0.11 mL (0.82 mmol) NEt₃ and 39 mg (0.34 mmol) 2-chloropyrimidine and the reaction
 5 heated at reflux for 3 days. The reaction was cooled, poured into 15 mL NaHCO₃ (sat.), extracted with CH₂Cl₂, washed with H₂O (2 x 100 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield an orange oil. The crude oil was triturated with EtOAc and Et₂O to give 25mg (23%) of (S)-N-[[3-[3-fluoro-4-{N-(2-pyrimidinyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a pale orange solid; mp 130-131°C, MS (CI) [M+H]⁺ 429.

Example 39

(S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide
 15



Compound 39

N-(Benzyloxyacetyl)-3-pyrrolidinol:

20 A solution of 4.4 mL (52.93 mmol) 3-pyrrolidinol in 250 mL CH₂Cl₂ at 0°C was added 8.4 mL (60.26 mmol) NEt₃ and 8.2 mL (51.97 mmol) benzyloxyacetyl chloride. The reaction was stirred for 3.5 h and then poured into 400 mL H₂O. The reaction was extracted with CH₂Cl₂, dried over MgSO₄, filtered and rotary evaporated to yield 12.0 g (98%) of N-(benzyloxyacetyl)-3-pyrrolidinol as a yellow
 25 oil.

1-[N-(Benzyloxyacetyl)pyrrolidinyl-3-oxy]-2-fluoro-4-nitrobenzene:

To a solution of 2.03 g (8.63 mmol) of N-(benzyloxyacetamide)-3-pyrrolidinol in 50 mL dry THF at 0°C was added dropwise 10 mL (10.0 mmol) 1M

KOtBu. After stirring at 0°C for 0.5 h, 0.96 mL (8.67 mmol) 3,4-difluoronitrobenzene was added and the reaction warmed to rt and stirred overnight. The reaction was poured into 100 mL H₂O and extracted with EtOAc. The combined organic layers were washed with H₂O, dried with MgSO₄, filtered, and the solvent removed by rotary evaporation. Then the solid was recrystallized from EtOAc and hexanes to afford 2.49 g (77%) of 1-[N-(benzyloxyacetyl)pyrrolidinyl-3-oxy]-2-fluoro-4-nitrobenzene as a solid.

1-[4-(N-Benzyloxyacetyl)pyrrolidinyl-3-oxy]-2-fluoro-4-aminobenzene:

To 1.61 g (4.31 mmol) of 1-[N-(benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-nitrobenzene in 50 mL EtOH was added 4.86 g (21.5 mmol) SnCl₂ and the reaction heated at 70°C for 2 h. The reaction was poured into ice water and extracted with EtOAc and CHCl₃ (2 x 100 mL). The combined organic layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give 880 mg (58%) of 1-[4-(N-benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-aminobenzene as a yellow oil. The material was used without further purification in the next step.

2-Fluoro-1-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}-4-(phenylmethoxy carbonylamino)benzene:

To 466 mg (2.73 mmol) of 1-[4-(N-benzyloxyacetyl)pyrrolidinyl-3-oxy]-2-fluoro-4-aminobenzene in 75 mL 2:1 acetone:H₂O at 0°C was added 527 mg (6.27 mmol) NaHCO₃ and 0.88 mL (2.56 mmol) Cbz-Cl. The reaction was allowed to warm to rt and stirred overnight. The volatiles were evaporated, the residue diluted with 200 mL H₂O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (EtOAc) afforded 473 mg (38%) of 3-fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}-1-(phenylmethoxycarbonylamino); MS (CI) [M+H]⁺ 479.

(R)-[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol:

To 473 mg (0.99 mmol) of 2-fluoro-1-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}-4-(phenylmethoxycarbonylamino)benzene in 25 mL dry THF at -78°C was added 0.55 mL (1.38 mmol) 2.5M *n*-BuLi and the reaction warmed to rt and stirred for 1 h. Then the solution was again cooled to -78°C and 0.19 mL (1.38 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred overnight. The reaction was carefully poured into 50 mL sat. NH_4Cl (aq.) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (0% to 10% MeOH in EtOAc) gave 107 mg (25%) of (R)-[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol as a gold oil; MS (CI) $[\text{M}+\text{Na}]^+$ 445.

(R)-[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

To 107 mg (0.24 mmol) of (R)-[3-[3-fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol in 50 mL CH_2Cl_2 at 0°C was added 0.07 mL (0.48 mmol) NEt_3 and 0.03 mL (0.34 mmol) methanesulfonyl chloride. After warming to rt and stirring for 1 h the reaction was diluted with 10 mL CH_2Cl_2 , washed with H_2O , dried over MgSO_4 , filtered and the solvent removed by rotary evaporation to yield (R)-[3-[3-fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate; MS (CI) $[\text{M}+\text{H}]^+$ 523.

(R)-[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide:

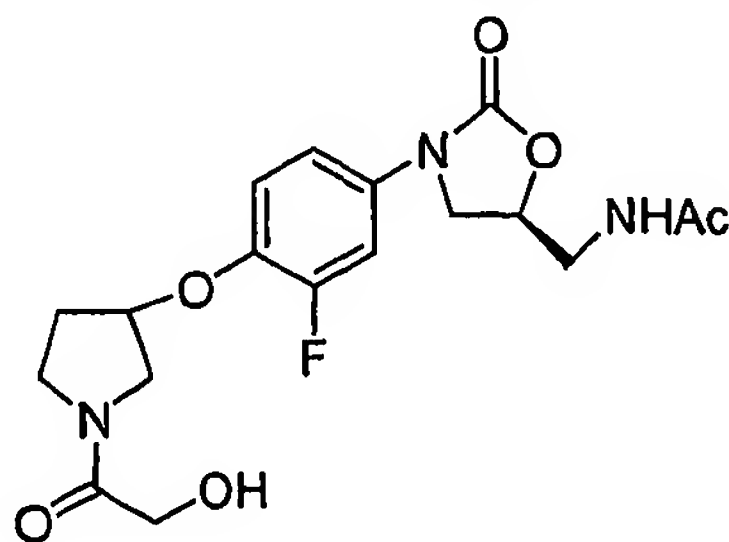
To a solution of 2.22 g (4.25 mmol) of (R)-[3-[3-fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate in 40 mL DMF was added 1.05 g (16.13 mmol) sodium azide and the reaction heated at 75°C overnight. Then the reaction was poured into 20 mL H_2O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O , dried over Na_2SO_4 , filtered, and the solvent removed by rotary evaporation to yield 1.29 g (65%) of (R)-[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide; MS (CI) $[\text{M}+\text{H}]^+$ 471.

(S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 39):

To a solution of 1.29 g (2.74 mmol) of (R)-[3-[3-fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL MeOH was added 1.38 mL (13.71 mmol) 1,3-propanedithiol and 1.91 mL (13.71 mmol) NEt₃ and the reaction stirred overnight at rt. Then 0.78 mL (8.23 mmol) acetic anhydride and 1.33 mL (16.45 mmol) pyridine were added and the reaction stirred at rt for 3 h. The reaction was filtered through a fritted funnel, rinsed with MeOH, and concentrated under reduced pressure. Then the residue was diluted with EtOAc, washed with H₂O (3 x 100 mL), washed with brine, dried over Na₂SO₄, and the solvent removed under reduced pressure to give an orange oil. Purification by silica gel chromatography (10% MeOH in EtOAc) gave 1.02 g (77%) of (S)-N-[[3-[3-fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam; mp 53-55°C, MS (CI) [M+H]⁺ 486.

Example 40

(S)-N-[[3-[3-Fluoro-4-{N-(α -hydroxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



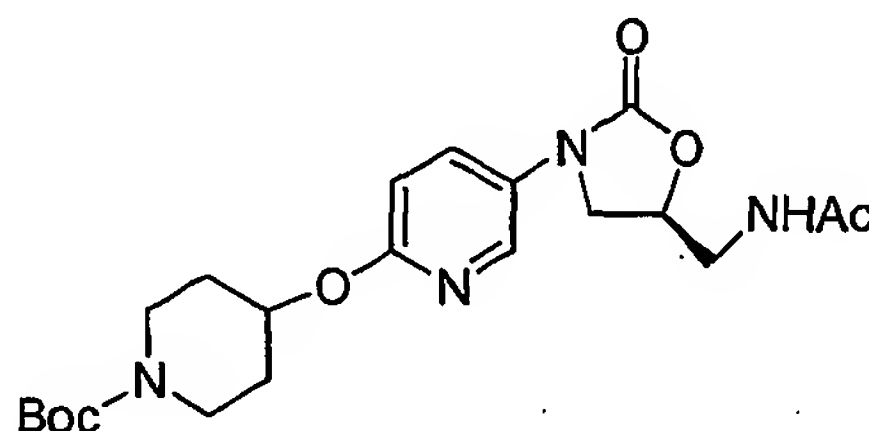
Compound 40

To a solution of 695 mg (1.43 mmol) of Compound 39 in 40 mL MeOH was added 451 mg (7.17 mmol) ammonium formate and a catalytic amount of 10% Pd/C, and the reaction was heated at reflux overnight. Then the reaction was filtered through a pad of celite and the solvent removed under reduced pressure. Trituration with EtOAc, MeOH, and hexanes afforded 363 mg (64%) of (S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-

oxazolidinyl)methyl]acetamide as a white powder; mp 97-99°C, MS (CI) $[M+H]^+$ 396.

Example 41

- 5 (5S)-3-[6-{N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy}-pyridin-3-yl]-
5-methylacetamide-oxazolidin-2-one



Compound 41

- 10 2-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-5-nitropyridine:

To a solution of 15.23 g (75.7 mmol) N-(*t*-butoxycarbonyl)-4-piperidinol in 450 mL THF at 0°C was added 126 mL (126 mmol) KO*t*Bu and the reaction stirred for 40 min. Then 10.0 g (63 mmol) 2-chloro-5-nitropyridine was added and the reaction warmed to rt and stirred overnight. The reaction was diluted with H₂O,
15 extracted with Et₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield the crude product as a black oil. Purification by silica gel chromatography (1:1 EtOAc:hexanes) gave the desired product; MS (CI) $[M+H]^+$ 324.

- 20 2-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-5-aminopyridine:

A solution of 280 mg (0.87 mmol) of 2-[N-(*t*-butoxycarbonyl)piperidinyl-4-oxy]-5-nitropyridine in 30 mL of EtOH was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi overnight. The suspension was filtered through celite and the filtrate evaporated under reduced pressure to afford crude
25 amine as a dark solid; MS (CI) $[M+H]^+$ 294.

2-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-5-(phenylmethoxy carbonylamino)pyridine:

To a solution of 5.4 g (18.4 mmol) of 2-[N-(*t*-butoxycarbonyl)piperidinyl-4-oxy]-5-aminopyridine in 300 mL 1:1 THF:H₂O was added 7.18 g (22.1 mmol)

cesium carbonate and 3.16 mL (22.1 mmol) benzylchloroformate and the reaction stirred at rt overnight. The mixture was diluted with H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give a dark solid. Purification by silica gel chromatography (4:1 hexanes:EtOAc) yielded 6.5 g (83%) of the carbamate as a yellow solid; MS (CI) [M+H]⁺ 428.

(R)-[3-[6-{N-(*t*-Butoxycarbonyl)piperdiny-4-oxy}pyridin-3-yl]-2-oxo-5-oxazolidinyl]methanol:

A solution of 5.17 g (12.1 mmol) of 2-{N-(*t*-butoxycarbonyl)piperdiny-4-oxy}-5-(phenylmethoxy carbonylamino)pyridine in 250 mL THF was cooled to –78°C and 5.32 mL (13.3 mmol) 2.5 M *n*BuLi was added and the solution stirred for 1 h. Then 1.89 mL (13.3 mmol) R-glycidyl butyrate was added and the reaction allowed to warm to rt and stirred overnight. The reaction was quenched with H₂O, extracted with Et₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield 4.22 g (88%) of the alcohol as a brown oil; MS (CI) [M+H]⁺ 394.

(R)-[3-[4-{N-(*t*-Butoxycarbonyl)piperdiny-4-oxy}pyridin-3-yl]-2-oxo-5-oxazolidinyl]methanesulfonate:

To a solution of 4.22 g (10.7 mmol) of (R)-[3-[6-{N-(*t*-butoxycarbonyl)piperdiny-4-oxy}pyridin-3-yl]-2-oxo-5-oxazolidinyl]methanol in 100 mL CH₂Cl₂ at 0°C was added 2.99 mL (21.4 mmol) NEt₃ and the reaction stirred for 45 min. Then 1.16 mL (15.0 mmol) methanesulfonylchloride was added and the reaction stirred at rt overnight. The reaction was quenched with H₂O, extracted with CH₂Cl₂, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield the mesylate as a brown solid.

(R)-[3-[4-{N-(*t*-Butoxycarbonyl)piperdiny-4-oxy}pyridin-3-yl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of (R)-[3-[6-{N-(*t*-butoxycarbonyl)piperdiny-4-oxy}pyridin-3-yl]-2-oxo-5-oxazolidinyl]methanesulfonate (10.7 mmol) in 100 mL DMF was added 2.78 g (42.8 mmol) sodium azide and the reaction heated at 75°C for 5 h. The reaction was cooled and the solvent removed under reduced pressure. The

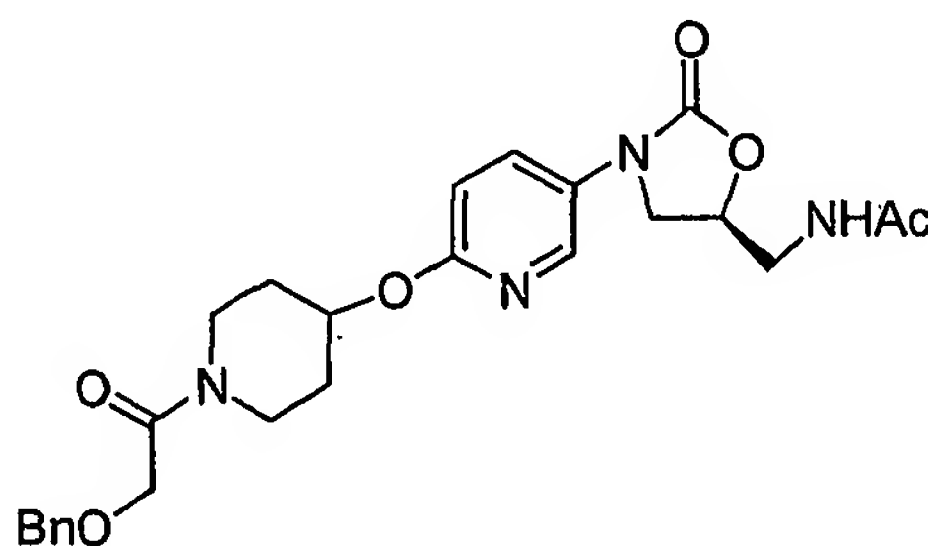
residue was diluted with H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield a brown oil which was used crude in the next reaction.

5 (5S)-3-[6-{N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one (Compound 41):

A solution of 3.3 g (7.9 mmol) of (R)-[3-[6-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}pyridin-3-yl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL of EtOAc was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi
 10 overnight. The suspension was filtered through celite and the filtrate evaporated under reduced pressure to afford crude amine as a dark solid. The crude reaction mixture was treated with 0.47 mL (5.8 mmol) pyridine and 2.39 mL (25 mmol) acetic anhydride and stirred overnight at rt. The volatiles were removed under reduced pressure to give a brown oil. Purification by silica gel chromatography
 15 (5% MeOH in EtOAc) yielded 1.7 g of (5S)-3-[6-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white foam; mp 99-101°C, MS (CI)[M+H]⁺ 435.

Example 42

20 (5S)-3-[6-{N-(Benzyloxyacetyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 42

25 (S)-3-[6-{N-(Piperidinyl-4-oxy)pyridin-3-yl]-2-oxo-5-oxazolidinyl] methyl]acetamide:

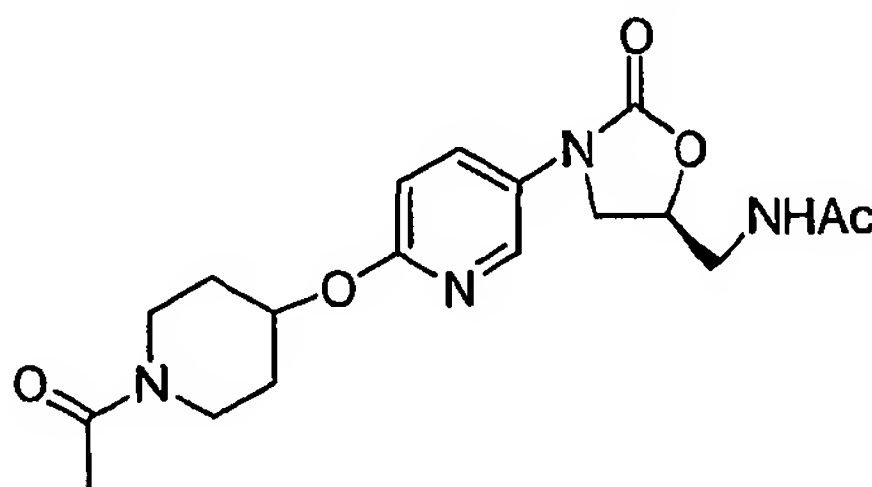
To a solution of 500 mg (1.1 mmol) of Compound 41 in 50 mL CH₂Cl₂ was added 0.88 mL (11.2 mmol) trifluoroacetic acid and the reaction stirred at rt for 3 days. The volatiles were removed under reduced pressure to give the TFA salt as a brown oil.

(5S)-3-[6-{N-(Benzyloxyacetyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one (Compound 42):

A solution of 99 mg (0.18 mmol) of (R)-3-[6-{N-(piperdiny-4-oxy)pyridin-3-yl}-2-oxo-5-oxazolidinyl] methyl]acetamide in 20 mL CH₂Cl₂ was treated with 0.12 mL (0.88 mmol) NEt₃ and the reaction stirred at rt for 30 min. Then 0.06 mL (0.36 mmol) benzoxyacetylchloride was added and the reaction stirred overnight. Then 100 mg of PS-Trisamine was added and the suspension stirred for 30 min. The reaction was filtered, quenched with 10 mL H₂O, extracted with CH₂Cl₂ (2 x 20 mL), dried over MgSO₄, and the solvent removed by rotary evaporation to give 31 mg of (5S)-3-[6-{N-(benzyloxyacetyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a tan semi-solid. ¹H NMR (CDCl₃) δ 8.13 (s, 1H); 7.98 (m, 1H); 7.35 (m, 5H); 6.72 (m, 1H); 6.59 (m, 1H); 5.25 (m, 1H); 4.82 (m, 1H); 4.61 (s, 2H); 4.24 (s, 2H); 3.90 (m, 1H); 3.77 (m, 2H); 3.70 (m, 1H); 3.68 (m, 2H); 3.54 (m, 1H); 3.41 (m, 1H); 2.08 (s, 3H); 2.05 (m, 2H); and 1.83 (m, 2H).

Example 43

(5S)-3-[6-{N-(Acetyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one

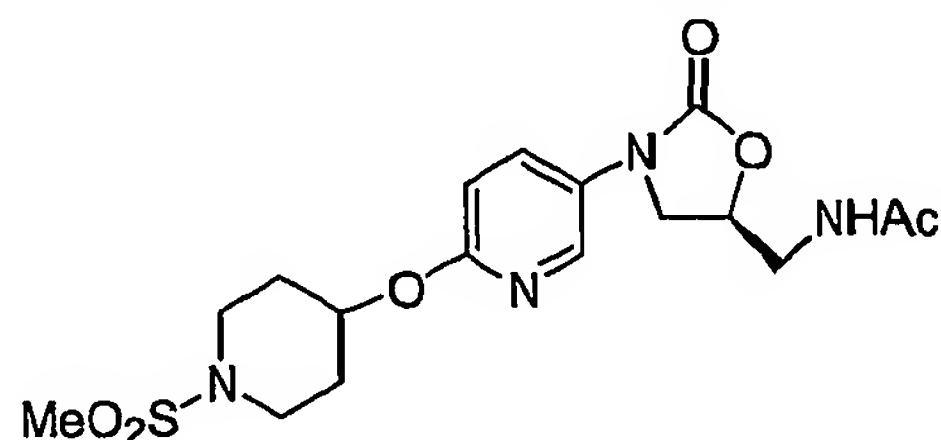


Compound 43

Compound 43 was prepared from 71 mg (0.13 mmol) of the TFA salt from Example 42, 0.09 mL (0.63 mmol) NEt₃, and 0.02 mL (0.26 mmol) acetyl chloride as described above to give 20 mg of (5S)-3-[6-{N-(acetyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white semi-solid. ¹H NMR (CDCl₃) δ 8.14 (m, 1H); 7.95 (m, 1H); 6.77 (s, 1H); 6.76 (brs, 1H); 5.25 (m, 1H); 4.83 (m, 1H); 4.06 (m, 1H); 3.91 (m, 1H); 3.80 (m, 1H); 3.68 (m, 3H); 3.4-3.6 (m, 2H); 2.15 (s, 3H); 2.04 (s, 3H); 2.02 (m, 2H); and 1.77 (m, 2H).

Example 44

(5S)-3-[6-{N-(Methanesulfonyl)piperidiny-4-oxy}-pyridin-3-yl]-
5-methylacetamide-oxazolidin-2-one

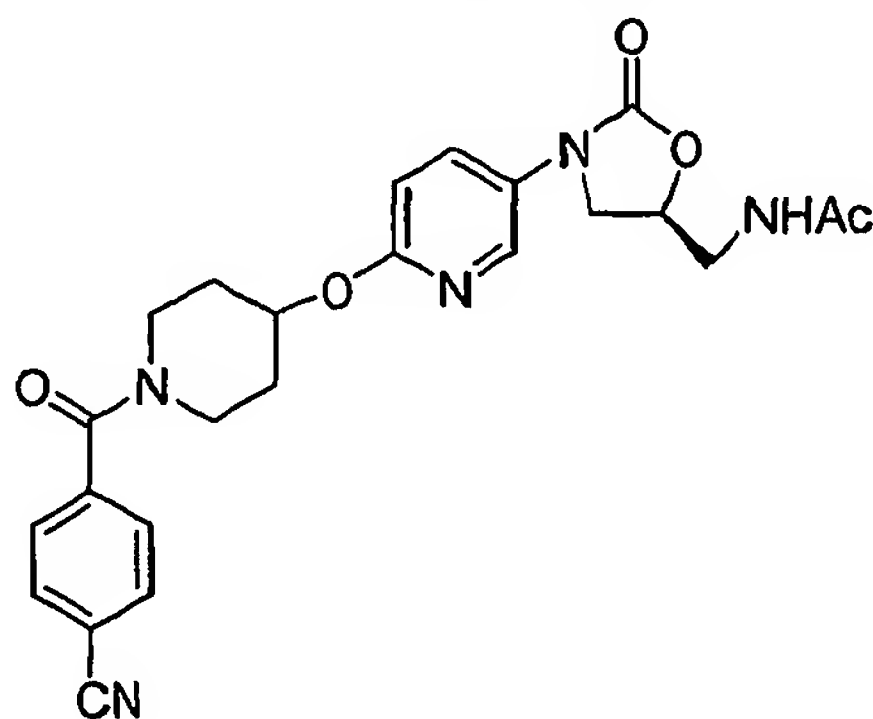


Compound 44

Compound 44 was prepared from 56 mg (0.10 mmol) of the TFA salt from Example 42, 0.07 mL (0.50 mmol) NEt₃, and 0.02 mL (0.20 mmol) methanesulfonyl chloride as described above to give 17 mg of (5S)-3-[6-{N-(methanesulfonyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white solid; mp 175-176°C, MS (CI) [M+H]⁺ 413.

Example 45

(5S)-3-[6-{N-(4-Cyanobenzoyl)piperidiny-4-oxy}-pyridin-3-yl]-
5-methylacetamide-oxazolidin-2-one



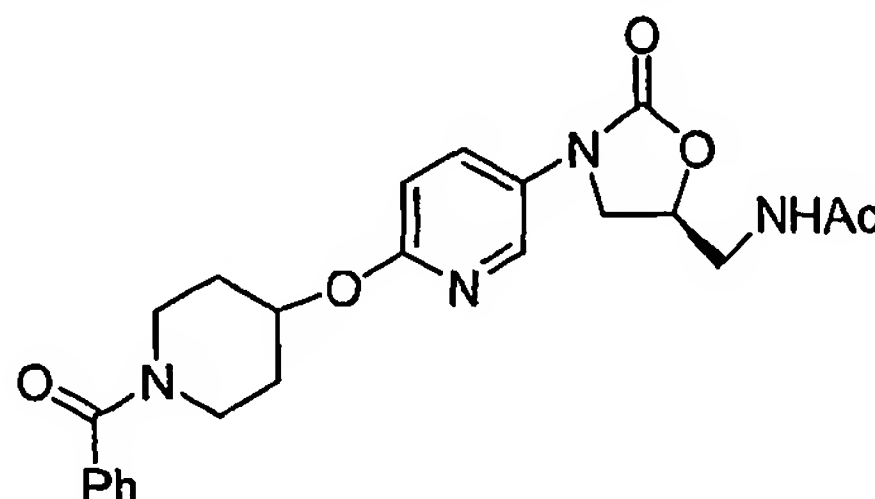
Compound 45

Compound 45 was prepared from 39 mg (0.07 mmol) of the TFA salt from Example 42, 0.05 mL (0.35 mmol) NEt₃, and 23 mg (0.14 mmol) 4-cyanobenzoyl chloride as described above to give 30 mg of (5S)-3-[6-{N-(4-cyanobenzoyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white semi-solid. ¹H NMR (CDCl₃) δ 8.13 (m, 1H); 7.97 (m, 1H); 7.69 (m, 2H); 7.57 (m,

2H); 6.78 (m, 1H); 6.48 (br t, 1H); 5.34 (m, 1H); 4.82 (m, 1H); 4.18 (m, 2H); 3.5-3.8 (m, 5H); 3.37 (m, 1H); 2.03 (s, 3H); 1.97 (m, 2H); and 1.82 (m, 2H).

Example 46

5 (5S)-3-[6-{N-(Benzoyl)piperidiny-4-oxy}-pyridin-3-yl]-
5-methylacetamide-oxazolidin-2-one



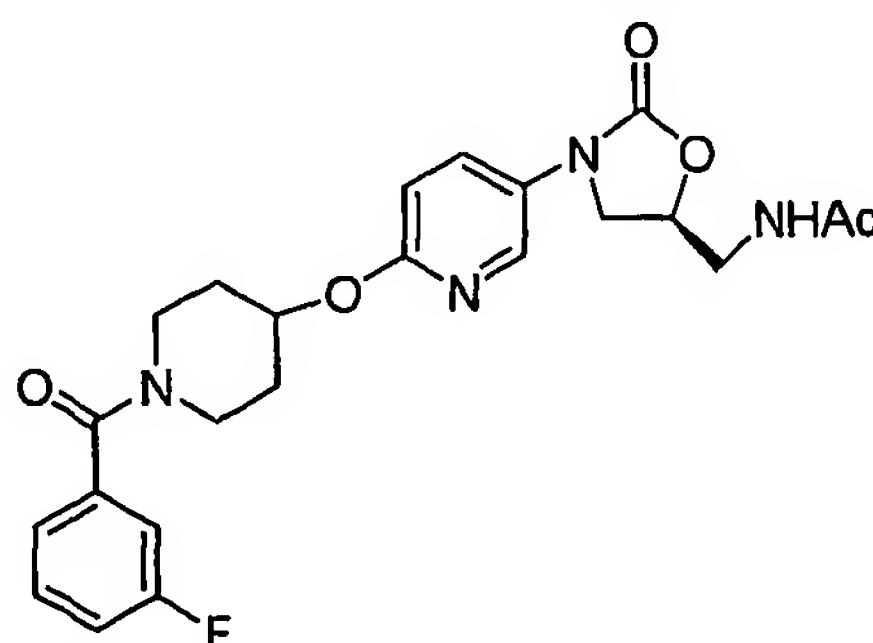
Compound 46

10 Compound 46 was prepared from 48 mg (0.09 mmol) of the TFA salt from Example 42, 0.06 mL (0.43 mmol) NEt₃, and 0.02 mL (0.20 mmol) benzoyl chloride as described above to give 50 mg of (5S)-3-[6-{N-(benzoyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a yellow solid; mp 180-182°C, MS (CI) [M+H]⁺ 439.

15

Example 47

(5S)-3-[6-{N-(3-Fluorobenzoyl)piperidiny-4-oxy}-pyridin-3-yl]-
5-methylacetamide-oxazolidin-2-one



Compound 47

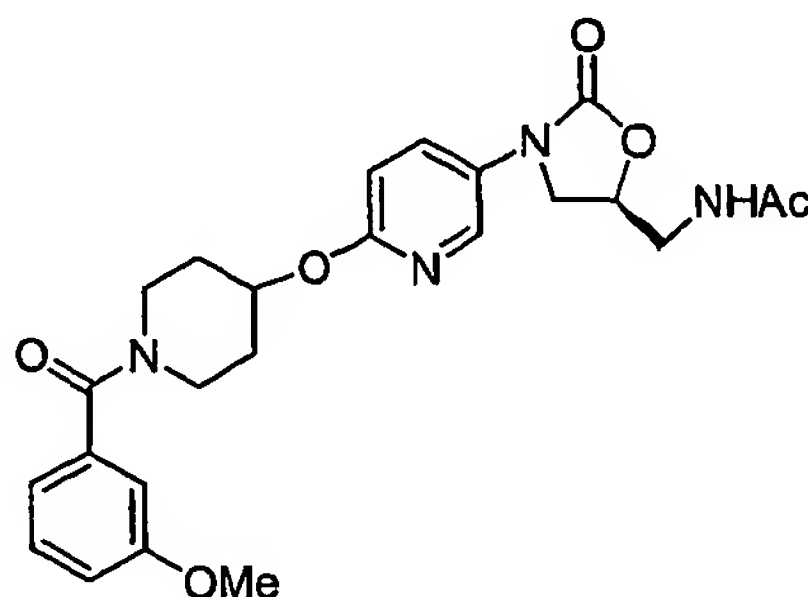
20

Compound 47 was prepared from 50 mg (0.12 mmol) of the TFA salt from Example 42, 0.08 mL (0.60 mmol) NEt₃, and 0.03 mL (0.24 mmol) 3-fluorobenzoyl chloride as described above to give 20 mg of (5S)-3-[6-{N-(3-

fluorobenzoyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a clear oil; MS (CI) $[M+H]^+$ 457.

Example 48

5 (5S)-3-[6-{N-(3-Methoxybenzoyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



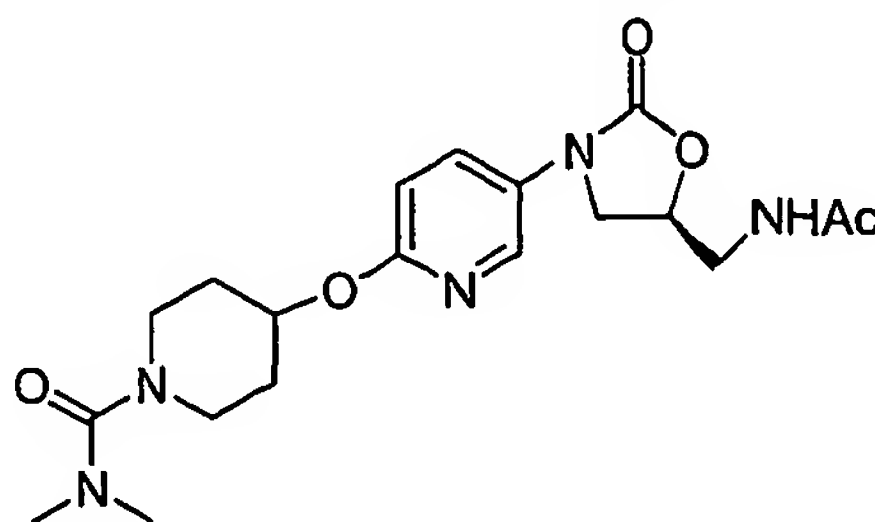
Compound 48

10 Compound 48 was prepared from 50 mg (0.12 mmol) of the TFA salt from Example 42, 0.08 mL (0.60 mmol) NEt_3 , and 0.03 mL (0.24 mmol) 3-methoxybenzoyl chloride as described above to give 20 mg of (5S)-3-[6-{N-(3-methoxybenzoyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a yellow oil; MS (CI) $[M+H]^+$ 468.

15

Example 49

(5S)-3-[6-{N-(Dimethylcarbamoyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 49

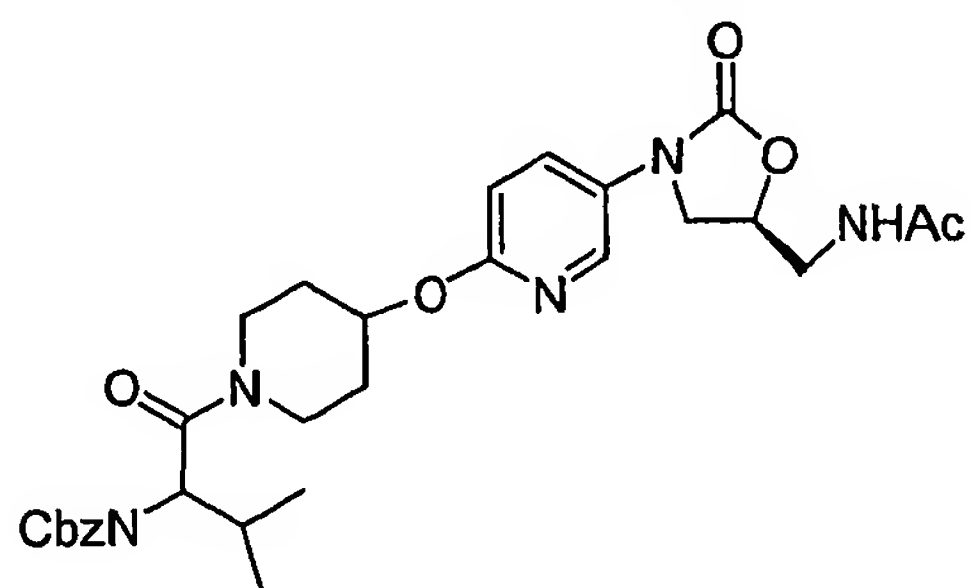
20

Compound 49 was prepared from 50 mg (0.12 mmol) of the TFA salt from Example 42, 0.08 mL (0.60 mmol) NEt_3 , and 0.02 mL (0.24 mmol) dimethylcarbamoyl chloride as described above to give 17 mg of (5S)-3-[6-{N-

(dimethylcarbamoyl) piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white semi-solid; MS (CI) $[M+H]^+$ 406.

Example 50

- 5 (5S)-3-[6-{N-(2-Benzoyloxycarbonyl-3-methylbutyryl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one

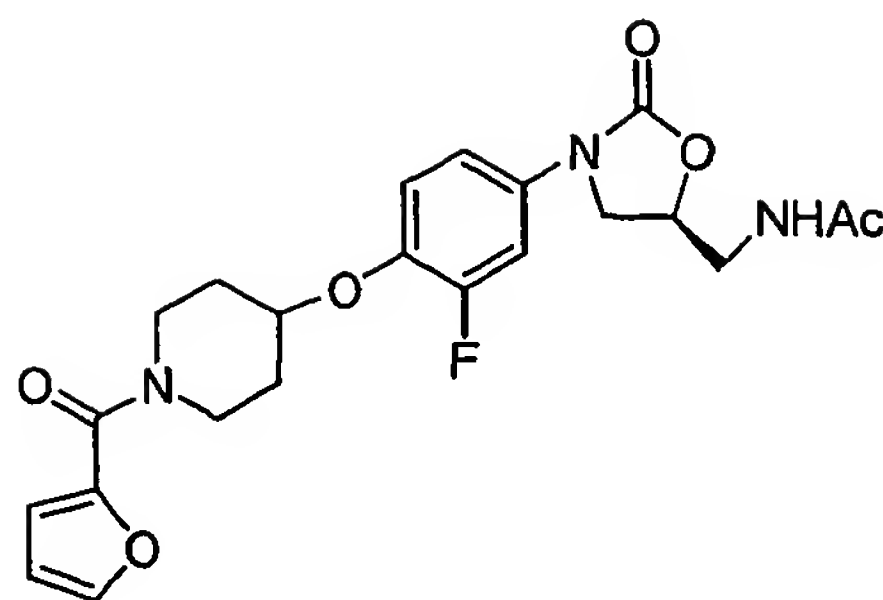


10 Compound 50

- To a solution of 36 mg (0.06 mmol) of the TFA salt from Example 42 in 20 mL CH_2Cl_2 was added 32 mg (0.13 mmol) Cbz-VAL-OH, 13 mg (0.07 mmol) EDCI, and 35 mg (0.25 mmol) HOBT. The reaction stirred at rt overnight. Then
- 15 the solution was washed with H_2O , extracted with CH_2Cl_2 , washed with sat. $NaHCO_3$, dried with $MgSO_4$ and concentrated to give 10 mg of (5S)-3-[6-{N-(2-Benzoyloxycarbonyl-3-methylbutyryl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a clear oil. 1H NMR ($CDCl_3$) δ 8.10 (m, 1H); 7.99 (m, 1H); 7.37 (m, 5H); 6.76 (m, 1H); 6.20 (m, 1H); 5.33 (s, 2H); 5.19 (m, 1H);
- 20 5.11 (m, 1H); 4.82 (m, 1H); 4.08 (m, 1H); 3.79 (m, 2H); 3.5-3.7 (m, 4H); 3.25 (m, 1H); 2.97 (m, 1H); 2.13 (m, 2H); 2.06 (s, 3H); 1.84 (m, 2H); and 1.30 (s, 6H).

Example 51

- 25 (S)-N-[[3-[3-Fluoro-4-{N-(2-furoyl)piperdiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

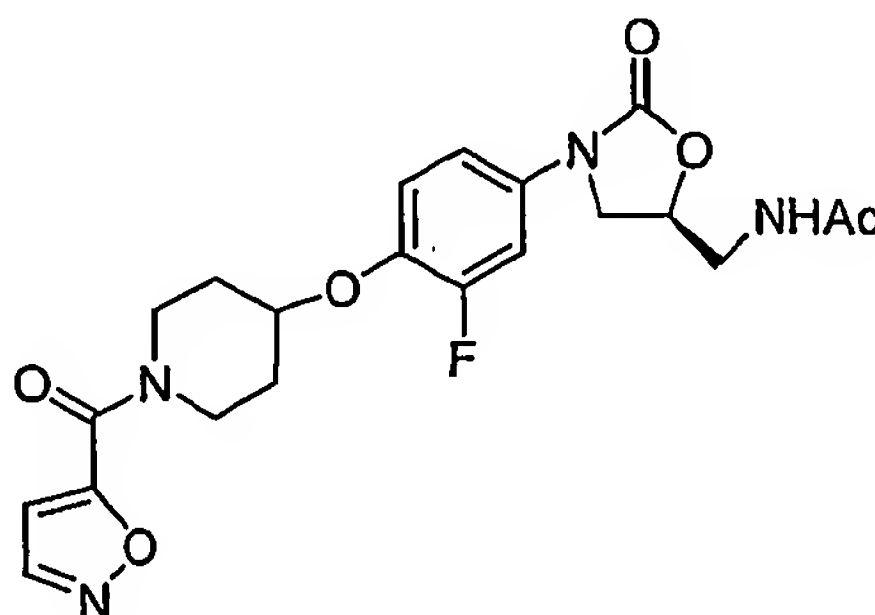


Compound 51

To a solution of 572 mg TFA salt in Example 2 in 50 mL CH₂Cl₂, was added
 5 1.2 mL triethylamine (TEA) and 0.20 mL 2-furanoyl chloride. The reaction was
 stirred for 18 hours under a nitrogen atmosphere. The reaction was poured into
 100 mL water and extracted. The organic layer was dried over MgSO₄, filtered
 and evaporated to an oil. This was triturated with warm ether to afford (S)-N-[[3-
 [3-fluoro-4-{N-(2-furoyl)piperdiny]oxy}phenyl]-2-oxo-5-
 10 oxazolidinyl]methyl]acetamide as a white solid; mp=134-136 °C; MS (CI) [M+H]⁺
 446.

Example 52

(S)-N-[[3-[3-Fluoro-4-{N-(5-isoxazolylcarbonyl)piperdiny]oxy}phenyl]-2-oxo-5-
 15 oxazolidinyl]methyl]acetamide



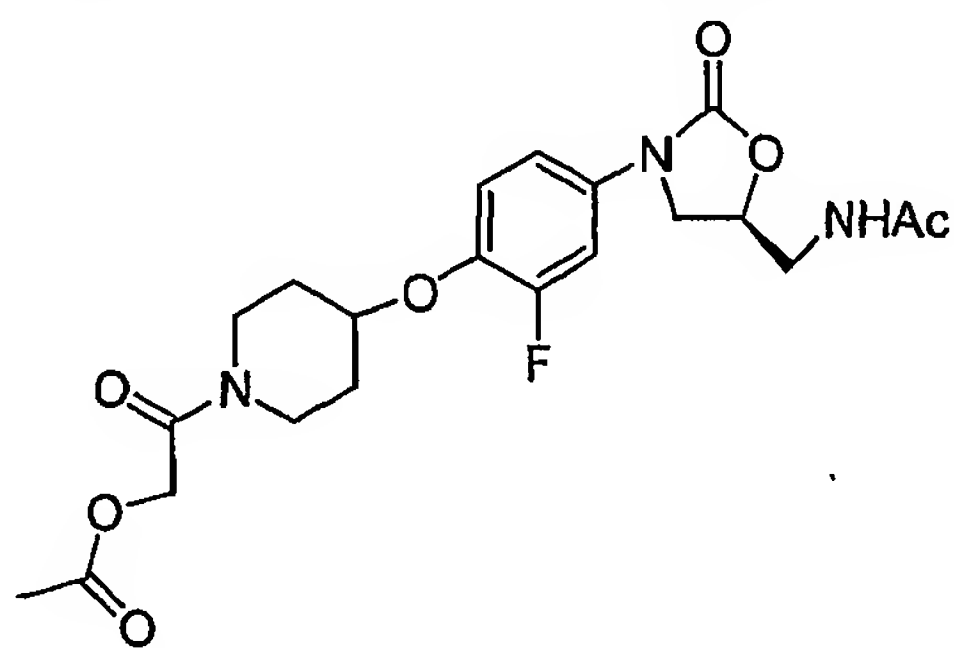
Compound 52

To 433 mg (3.83 mmoles) of 5-isoxazole carboxylic acid in 10 mL CH₂Cl₂,
 20 was added 1 drop of DMF followed by 2 mL oxalyl chloride (2M in CH₂Cl₂; 4
 mmoles). After stirring for 0.5 hour, a solution of 895 mg (1.92 mmoles) TFA salt
 in Example 2 and 1 mL of TEA in 5 mL CH₂Cl₂ was added. The reaction was dried
 over MgSO₄, filtered and evaporated. This was purified by column
 chromatography with 5% MeOH/CH₂Cl₂ as the eluant to afford (S)-N-[[3-[3-fluoro-

4-{N-(5-isoxazolylcarbonyl)piperdiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam. ¹H NMR (CDCl₃) δ 8.31 (d, J=1.8 Hz, 1H), 7.49 (dd, J=12.9, 2.6 Hz, 1H), 7.08-7.12 (m, 1H), 7.01 (t, J=8.8 Hz, 1H), 6.77 (d, J=1.8 Hz, 1H), 6.04 (t, J=6.0 Hz, 1H), 4.73-4.81 (m, 1H), 4.52-4.57 (m, 1H), 4.03 (t, J=9.0 Hz, 1H), 3.56-3.95 (m, 7H), 2.03 (s, 3H), 1.75-2.00 (m, 4H). MS (CI) [M+H]⁺ 447.

Example 53

(S)-N-[[3-[3-Fluoro-4-{N-(acetoxycetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

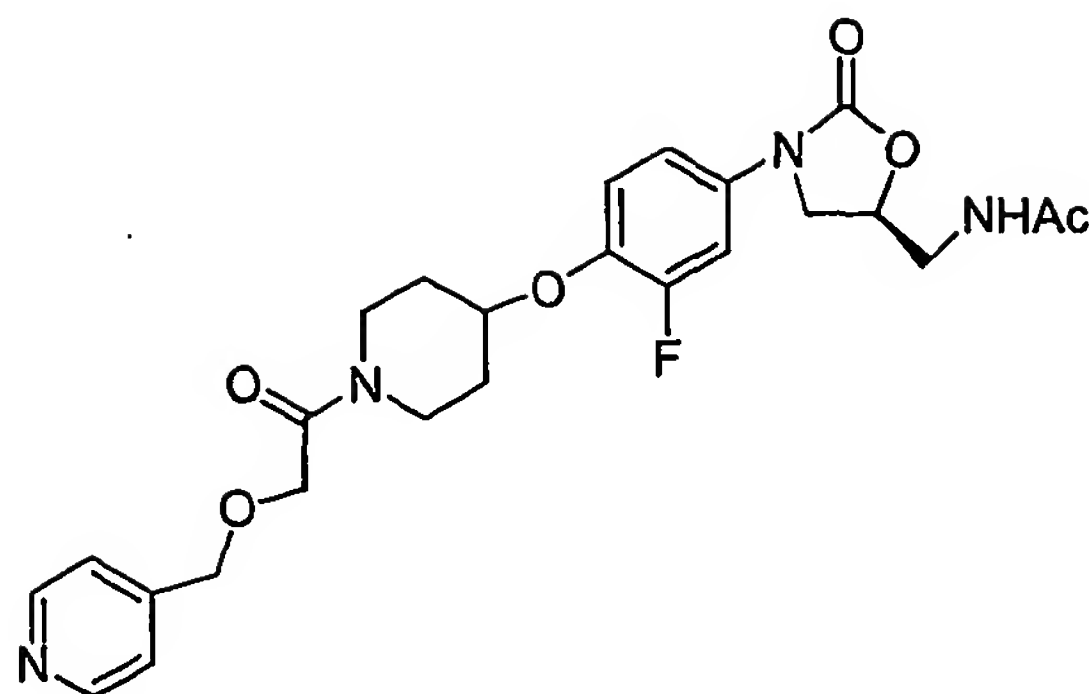


Compound 53

To 2.12 g (4.55 mmol) of TFA salt of Example 2 in 150 mL CH₂Cl₂, was added 5 mL TEA. After stirring for 15 min, 0.62 (5.76 mmol) acetoxycetyl chloride was added and the reaction stirred for 2.5 h. The volatiles were evaporated and the residue chromatographed using 10% MeOH/ CH₂Cl₂ as the eluant. (S)-N-[[3-[3-Fluoro-4-{N-(acetoxycetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide was isolated as a pale beige solid; mp=146-147.5°C, MS (CI) [M+H]⁺ 452.

Example 54

(S)-N-[[3-[4-{N-(Pyridin-4-ylmethoxyacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 54

(S)-N-[[3-[4-{N-(Chloroacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide:

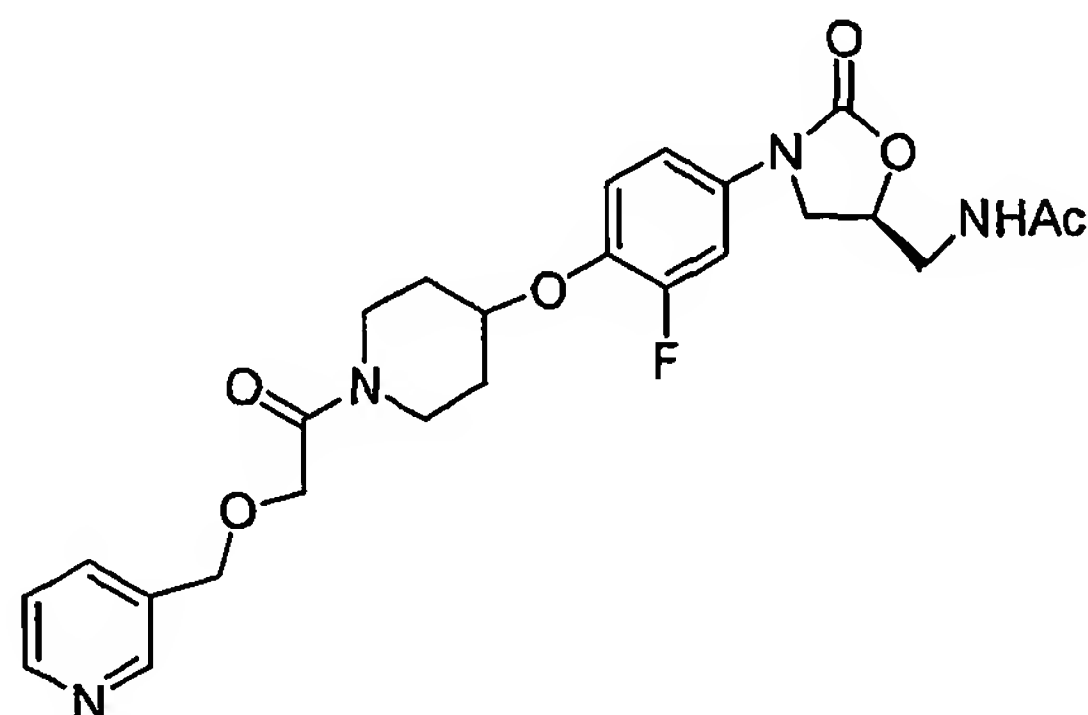
A solution of 4.19 g (9.00 mmol) of TFA salt of Example 2 and 3 mL of TEA in 125 mL CH₂Cl₂ was added dropwise to 0.75 mL of chloroacetylchloride (9.42 mmol) in 100 mL CH₂Cl₂. After stirring at room temperature for 2 h, the reaction was poured into 300 mL water and extracted. The organic layer was dried over MgSO₄, filtered and evaporated to give (S)-N-[[3-[4-{N-(Chloroacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide as a viscous oil.

(S)-N-[[3-[4-{N-(Pyridin-4-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (Compound 54):

To 101.1 mg NaH (60% in oil; 2.53 mmol) in 5 mL anh THF at 0°C, was added dropwise 265 mg (2.43 mmol) pyridine-4-methanol in 5 mL anh THF. After stirring for 15 min, 503 mg (1.18 mmol) (S)-N-[[3-[4-{N-(chloroacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]-methylacetamide in 5 mL anh THF was added. The reaction was stirred at room temperature for 16 h, and then poured into 125 mL water. This was extracted with 3 x 100 mL CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and evaporated. Pure (S)-N-[[3-[4-{N-(pyridin-4-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide, obtained by chromatography using 5% MeOH/CH₂Cl₂, was isolated as a white foam. ¹H NMR (CDCl₃) δ 8.59 (d, J=5.9 Hz, 2H), 7.47 (dd, J=12.9, 2.6 Hz, 1H), 7.28 (d, J=5.9 Hz, 2H), 7.07-7.11 (m, 1H), 6.99 (t, J=8.8 Hz, 1H), 5.91-5.94 (m, 1H), 4.72-4.79 (m, 1H), 4.65 (s, 2H), 4.45-4.49 (m, 1H), 4.26 (s, 2H), 4.02 (t, J=8.9 Hz, 1H), 3.40-3.78 (m, 7H), 2.02 (s, 3H), 1.85-1.95 (m, 4H). MS (CI) [M+H]⁺ 501.

Example 55

(S)-N-[[3-[4-{N-(Pyridin-3-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

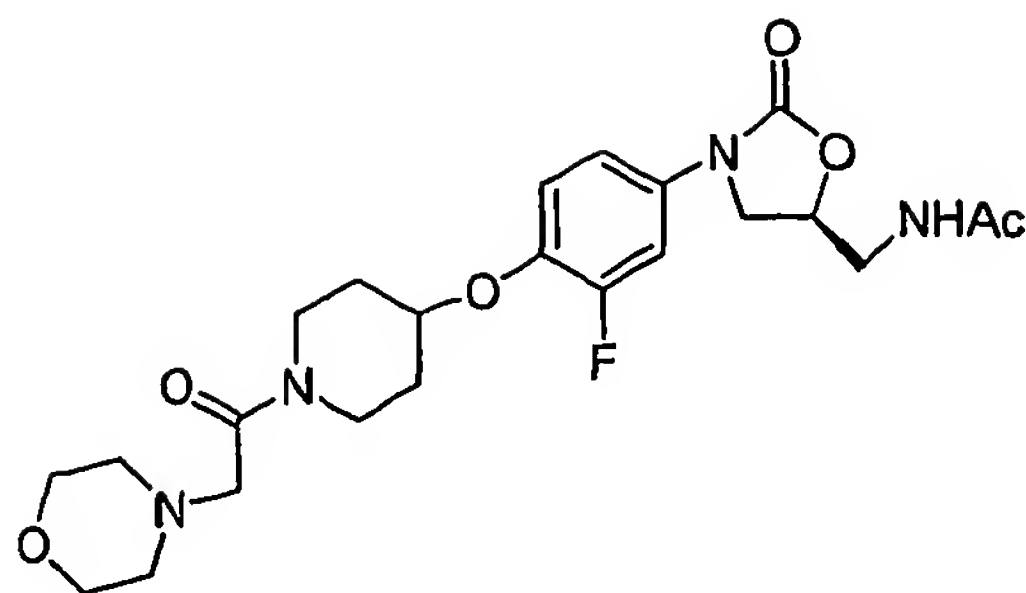


Compound 55

To 117 mg NaH (60% in oil; 2.93 mmol) in 5 mL anh THF at 0°C, was added dropwise 0.24 mL (2.47 mmol) pyridine-3-methanol in 5 mL THF. After stirring for 15 minutes, 523 mg (1.22 mmol) chloroacetamide from Example 54 in 5 mL anh THF was added in one portion. The reaction was warmed to room temperature and stirred for 72 hours. The reaction was poured into 50 mL water and extracted 3 x 75 mL CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and evaporated. Chromatography with 3% MeOH/CH₂Cl₂ afforded (S)-N-[[3-[4-{N-(pyridin-3-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide as a clear glass. ¹H NMR (CDCl₃) δ 8.56-8.60 (m, 2H), 7.73 (d, J=7.8 Hz, 1H), 7.47 (dd, J=13.0, 2.6 Hz, 1H), 7.30 (dd, J=7.8, 5.1 Hz, 1H), 7.08 (dd, J=8.9, 1.6 Hz, 1H), 6.99 (t, J=8.9 Hz, 1H), 6.02 (t, J=6.2 Hz, 1H), 4.70-4.78 (m, 1H), 4.64 (s, 2H), 4.43-4.47 (m, 1H), 4.24 (s, 2H), 4.02 (t, J=8.9 Hz, 1H), 3.57-3.78 (m, 6H), 3.35-3.45 (m, 1H), 2.02 (s, 3H), 1.80-1.96 (m, 4H). MS (CI) [M+H]⁺ 501.

Example 56

(S)-N-[[3-[4-{N-(Morpholinoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide



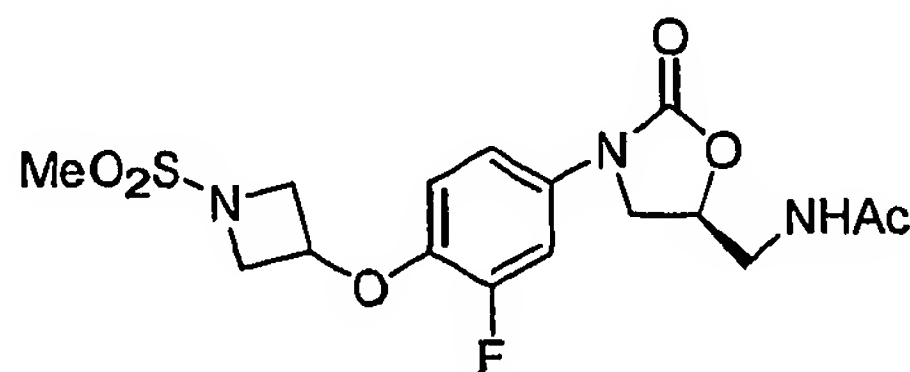
Compound 56

To 415 mg (0.97 mmol) of chloroacetamide from Example 54 in 15 mL THF, was added 0.25 mL (2.87 mmol) morpholine. The reaction was stirred for 72 hours at room temperature, poured into 50 mL water and extracted 3 x 50 mL CH₂Cl₂. The combined organic layers were washed with water, dried over MgSO₄, filtered and evaporated. (S)-N-[[3-[4-{N-Morpholinoacetyl}-piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide was obtained as a clear glass after chromatography (3% MeOH/CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.47 (dd, J=13.0, 2.6 Hz, 1H), 7.07-7.11 (m, 1H), 7.00 (t, J=8.8 Hz, 1H), 5.93 (br t, J=6.1 Hz, 1H), 4.73-4.79 (m, 1H), 4.44-4.78 (m, 1H), 4.02 (t, J=9.0 Hz, 1H), 3.51-3.85 (m, 11H), 3.20 (s, 2H), 2.47-2.51 (m, 4H), 2.03 (s, 3H), 1.81-1.96 (m, 4H). MS (CI) [M+H]⁺ 479.

15

Example 57

(S)-N-[[3-[3-Fluoro-4-{N-(methanesulfonyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



20

Compound 57

1-[N-(Diphenylmethyl)azetidiny-3-oxy]-2-fluoro-4-nitrobenzene:

To 5.40 g (22.56 mmol) N-(diphenylmethyl)azetidin-4-ol in 200 mL THF at 0°C, was added 30 mL KOtBu (1M in THF; 30 mmol). After stirring for 0.5 h, 2.5 mL (22.58 mmol) 3,4-difluoronitrobenzene was added. The reaction was warmed to room temperature and stirred for 18 h. After evaporation of the THF, the

25

residue was partitioned between 300 mL water and 250 mL CH₂Cl₂. The aqueous was washed with additional CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and evaporated. Chromatography with 15% EtOAc/hexanes afforded pure 1-[N-(Diphenylmethyl)azetidiny-4-oxy]-2-fluoro-4-nitrobenzene as a viscous gold oil. ¹H NMR (CDCl₃) δ 7.96-8.01 (m, 2H), 7.16-7.47 (m, 10H), 6.72-6.80 (m, 1H), 4.88-5.00 (m, 1H), 4.94 (s, 1H), 3.70-3.81 (m, 2H), 3.17-3.27 (m, 2H). MS (CI) [M+H]⁺ 379.

1-[N-(Diphenylmethyl)azetidiny-3-oxy]-2-fluoro-4-aminobenzene:

7.55 g (19.95 mmol) 1-[N-(diphenylmethyl)azetidiny-4-oxy]-2-fluoro-4-nitrobenzene, 7.31 g (116 mmol) ammonium formate, and approximately 250 mg 10% Pd/C in 500 mL MeOH were heated at reflux for 21 h. After cooling, the reaction was filtered through a pad of Celite and the methanol evaporated to afford crude 1-[N-(diphenylmethyl)azetidiny-4-oxy]-2-fluoro-4-aminobenzene as a mustard yellow semisolid. ¹H NMR (CDCl₃) δ 7.13-7.48 (m, 10H), 6.57 (t, J=8.8 Hz, 1H), 6.43 (dd, J=12.9, 2.6 Hz, 1H), 6.23-6.30 (m, 1H), 4.67-4.80 (m, 1H), 4.52 (s, 1H), 4.00 (br s, 2H), 3.73-3.85 (m, 2H), 3.13-3.23 (m, 2H). MS (CI) [M+H]⁺ 349.

2-Fluoro-1-{N-(diphenylmethyl)azetidiny-3-oxy}-4-(benzyloxycarbonylamino)-benzene:

Crude aniline (6.19 g; 17.77 mmol) in 750 mL of acetone/water (2:1) was cooled to 0°C. 3.34 g (39.76 mmol) sodium bicarbonate was added followed by 3.3 mL (23.39 mmol) benzylchloroformate. The reaction was stirred at room temperature for 20 h and the volatiles were evaporated. The aqueous residue was extracted 3 x 250 mL EtOAc. The combined organic layers were dried over MgSO₄, filtered and evaporated. Chromatography with 50% EtOAc/hexanes afforded pure 2-fluoro-1-{N-(diphenylmethyl)azetidiny-3-oxy}-4-(benzyloxycarbonylamino)benzene as a white solid; mp=128-131°C; MS (CI) [M+H]⁺ 483.

(R)-[3-[3-Fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol:

To 2.13 g (4.41 mmol) of 2-fluoro-1-{N-(diphenylmethyl)azetidiny-3-oxy}-4-(benzyloxycarbonylamino)benzene in 75 mL of THF at -78°C under a nitrogen atmosphere, was added 2.5 mL nBuLi (2.5 M in hexanes; 6.25 mmol). The reaction was stirred for 0.5 h and then 0.65 mL of (R)-glycidyl butyrate (4.59 mmol) was added. The reaction was stirred at room temperature overnight, poured into 75 mL of saturated ammonium chloride (aq) and extracted 3 x 100 mL EtOAc. The combined organic layers were washed with water, dried over MgSO₄, filtered and evaporated. Chromatography with 60% EtOAc/hexanes afforded (R)-[3-[3-Fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidiny]methanol as an off-white foam. ¹H NMR (CDCl₃) δ 7.17-7.51 (m, 11H), 7.03 (d, J=8.9 Hz, 1H), 6.70 (t, J=8.9 Hz, 1H), 4.70-4.90 (m, 2H), 4.44 (s, 1H), 3.87-4.13 (m, 3H), 3.68-3.76 (m, 3H), 3.13-3.18 (m, 2H), 2.05 (br t, 1H). MS (CI) [M+H]⁺ 449.

15 (S)-[3-[3-Fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidiny]methyl azide:

To 1.40 g (3.12 mmol) of (R)-[3-[3-fluoro-4-{N-(diphenylmethyl)-azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidiny]methanol and 0.90 mL (6.46 mmol) TEA in 90 mL CH₂Cl₂ at 0°C under a nitrogen atmosphere, was added 0.3 mL (3.87 mmol) methanesulfonyl chloride. After stirring for 1.5 h, the reaction was poured into 150 mL water and extracted. The aqueous layer was washed with an additional portion of CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and evaporated to give crude mesylate. MS (CI) [M+H]⁺ 527. This mesylate (3.08 mmol) and 0.80 g (12.31 mmol) sodium azide in 75 mL DMF were heated at 70°C for 2.5 hours under a nitrogen atmosphere. After cooling, the reaction was poured into 400 mL water and extracted 3 x 150 mL EtOAc. The combined organic layers were washed with several portions of water, dried over MgSO₄, filtered and evaporated to yield (R)-[3-[3-fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidiny]methyl azide as a semi-solid. ¹H NMR (CDCl₃) δ 7.19-7.50 (m, 11H), 7.05 (d, J=9.0 Hz, 1H), 6.74 (t, J=9.0 Hz, 1H), 4.71-4.87 (m, 2H), 4.46 (s, 1H), 4.03 (t, J=8.8 Hz, 1H), 3.50-3.88 (m, 5H), 3.10-3.21 (m, 2H). MS [M+H]⁺ 474.

(S)-[3-[3-Fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide:

5 1.13 g (2.39 mmol) (R)-[3-[3-Fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl azide and 0.85 g (3.24 mmol) triphenylphosphine in 60 mL THF were stirred at room temperature under a nitrogen atmosphere overnight. 3.0 mL water was added and the reaction heated at 70°C for 6 h. The volatiles were evaporated and the remaining water
10 azeotroped with several portions of benzene to give a mixture of crude amine and triphenylphosphine oxide. MS (CI) [M+H]⁺ 448. The crude amine, 0.3 mL (3.17 mmol) acetic anhydride and 0.6 mL (7.42 mmol) pyridine in 75 mL EtOAc were stirred at room temperature under a nitrogen atmosphere overnight. The reaction was extracted with 100 mL water. The organic layer was dried over MgSO₄,
15 filtered and evaporated. Chromatography with 2% MeOH/CH₂Cl₂ afforded (S)-[3-[3-Fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide as a white foam. ¹H NMR (CDCl₃) δ 7.13-7.50 (m, 11H), 6.92-7.03 (m, 1H), 6.70 (t, J=8.9 Hz, 1H), 5.96 (br s, 1H), 4.68-4.85 (m, 2H), 4.45 (s, 1H), 3.97 (t, J=9.0 Hz, 1H), 3.50-3.76 (m, 5H), 3.10-3.19 (m, 2H), 2.03 (s,
20 3H). MS (CI) [M+H]⁺ 490.

(S)-N-[[3-[3-Fluoro-4-{N-(methanesulfonyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 57):

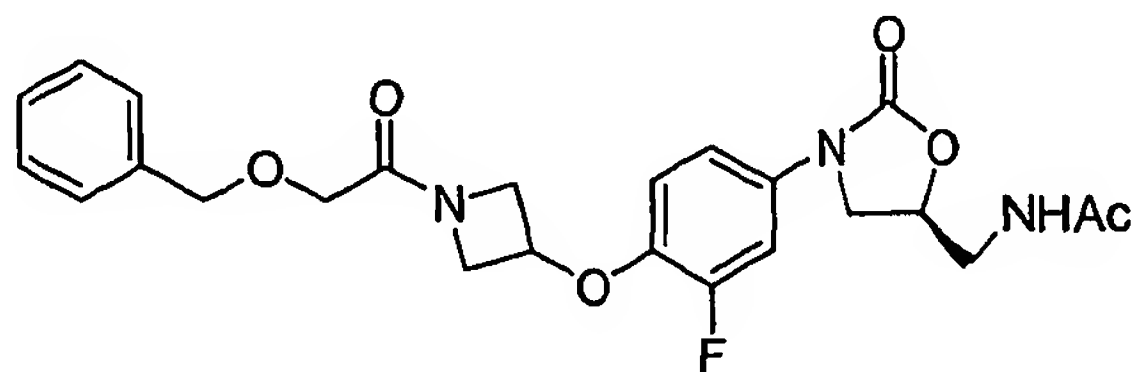
25 To 160 mg (0.327 mmol) (S)-[3-[3-fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide in 5 mL 1,2-dichloroethane, was added 0.04 mL (0.371 mmol) α-chloroethylchloroformate. The reaction was heated at 70°C for 5 h. Ten mL MeOH was added and reflux continued overnight. The volatiles were evaporated to afford the crude hydrochloride salt of the
30 deprotected amine. This was suspended in 20 mL CH₂Cl₂ and 0.15 mL (1.07 mmol) TEA was added followed by 0.1 mL (1.29 mmol) methanesulfonyl chloride. The reaction was stirred overnight, poured into 100 mL water and extracted. The organic layer was washed with 1N HCl (aq), dried over MgSO₄, filtered and

evaporated. Chromatography with 3% MeOH/CH₂Cl₂ afforded (S)-N-[[3-[3-fluoro-4-{N-(methanesulfonyl)azetidiny-3-oxy}phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide as a white foam. ¹H NMR (CDCl₃) δ 7.52 (dd, J=13.1, 2.7 Hz, 1H), 7.06-7.10 (m, 1H), 6.76 (t, J=8.9 Hz, 1H), 5.91 (br t, 1H), 4.87-4.95 (m, 1H), 4.72-4.81 (m, 1H), 4.28 (dd, J=9.7, 6.4 Hz, 2H), 4.09 (dd, J=9.7, 4.8 Hz, 2H), 4.01 (t, J=8.9 Hz, 1H), 3.56-3.77 (m, 3H), 2.93 (s, 3H), 2.02 (s, 3H). MS (CI) [M+H]⁺ 402.

Example 58

10 (S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

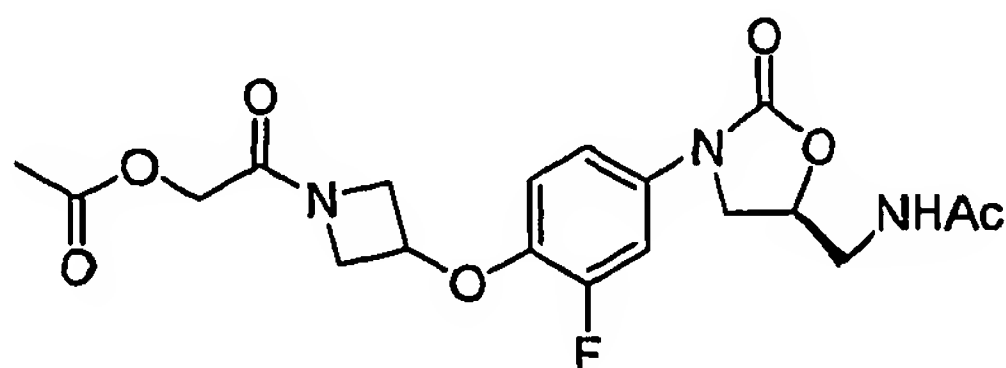


Compound 58

258 mg (0.527 mmol) (S)-[3-[3-fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide from Example 57 and 0.20 mL (1.26 mmol) benzyloxyacetyl chloride in 10 mL 1,2-dichloroethane were heated at reflux for 48 h under a nitrogen atmosphere. After cooling, the reaction was diluted with 100 mL CH₂Cl₂ and extracted with 50 mL 1N HCl. The organic layer was washed with water, dried over MgSO₄, filtered and evaporated. Chromatography with 3% MeOH/CH₂Cl₂ yielded (S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white powder; mp=119-121°C; MS (CI) [M+H]⁺ 472.

Example 59

25 (S)-N-[[3-[3-Fluoro-4-{N-(acetoxycetyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

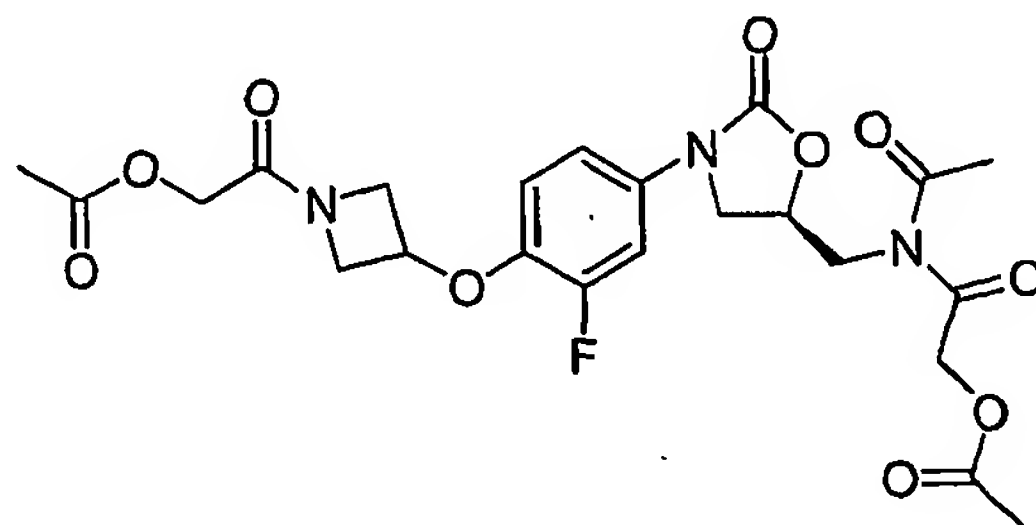


Compound 59

323 mg (0.660 mmol) (S)-[3-[3-fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide from Example 57 and 0.2 mL (1.86 mmol) acetoxyacetyl chloride in 15 mL 1,2-dichloroethane were heated at reflux for 24 h. After cooling, the volatiles were evaporated and the residue chromatographed with 3% MeOH/CH₂Cl₂. (S)-N-[[3-[3-Fluoro-4-{N-(acetoxyacetyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide was isolated as a white solid; mp=172-175°C; MS (CI) [M+H]⁺ 424.

Example 60

(S)-N-[[3-[3-Fluoro-4-{N-(acetoxyacetyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]-N-[α-acetoxyacetyl]acetamide

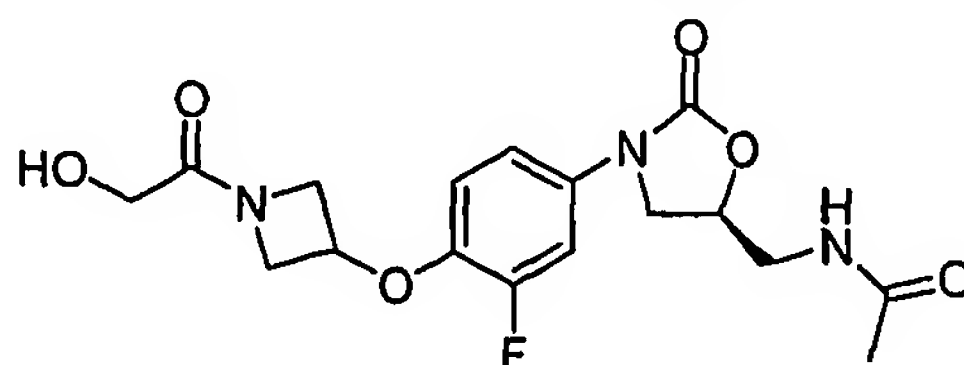


Compound 60

This was also isolated (as a white foam) from the reaction mixture in Example 59. ¹H NMR (CDCl₃) δ 7.53 (dd, J=13.0, 2.8 Hz, 1H), 7.04-7.10 (m, 1H), 6.78 (t, J=8.8 Hz, 1H), 4.95-5.18 (m, 3H), 4.75-4.89 (m, 1H), 4.30-4.68 (m, 5H), 4.00-4.30 (m, 3H), 3.83-3.91 (m, 1H), 3.68-3.79 (m, 1H), 2.47 (s, 3H), 2.02 (s, 3H), 2.18 (s, 3H). MS (CI) [M+Na]⁺ 546.

Example 61

(S)-N-[[3-[3-Fluoro-4-{N-(α-hydroxyacetyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 61

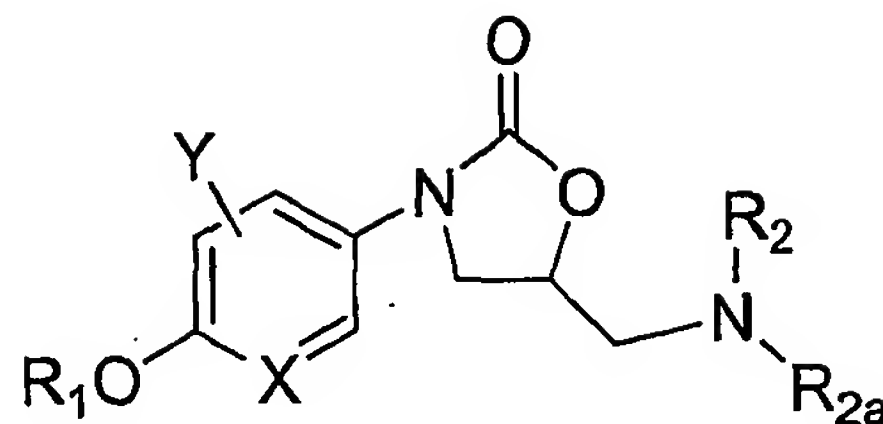
150 mg (0.354mmol) (S)-N-[[3-[3-Fluoro-4-{N-(acetoxyacetyl)azetidiny-3-
oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide from Example 59 and 55 mg
potassium carbonate in 30 mL MeOH were stirred at room temperature for 20
minutes under a nitrogen atmosphere. The volatiles were evaporated and the
5 sample dissolved in 50 mL CH₂Cl₂. This was washed with 50 mL water, dried
over MgSO₄, filtered and evaporated to afford (S)-N-[[3-[3-fluoro-4-{N-(α -
hydroxyacetyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as
a white solid, mp=158-160°C; ¹H NMR (MeOH-d₄) δ 7.57 (dd, J=13.3, 2.6 Hz, 1H),
7.15-7.18 (m, 1H), 6.91 (t, J=9.0 Hz, 1H), 5.04-5.12 (m, 1H), 4.66-4.80 (m, 2H),
10 4.44 (dd, J=10.6, 6.7 Hz, 1H), 4.27-4.34 (m, 1H), 4.01-4.11 (m, 4H), 3.78 (dd,
J=9.2, 6.4 Hz, 1H), 3.55 (d, J=5.0 Hz, 2H), 1.96 (s, 3H). MS (CI) [M+H]⁺ 382.

15

The invention has been described in detail with particular reference to the
above embodiments thereof. The above embodiments and examples are given to
illustrate the scope and spirit of the present invention. These embodiments and
examples will make apparent, to those skilled in the art, other embodiments and
20 examples. These other embodiments and examples are within the contemplation
of the present invention. It will be understood that variations and modifications
can be effected within the spirit and scope of the invention; therefore, the instant
invention should be limited only by the appended claims.

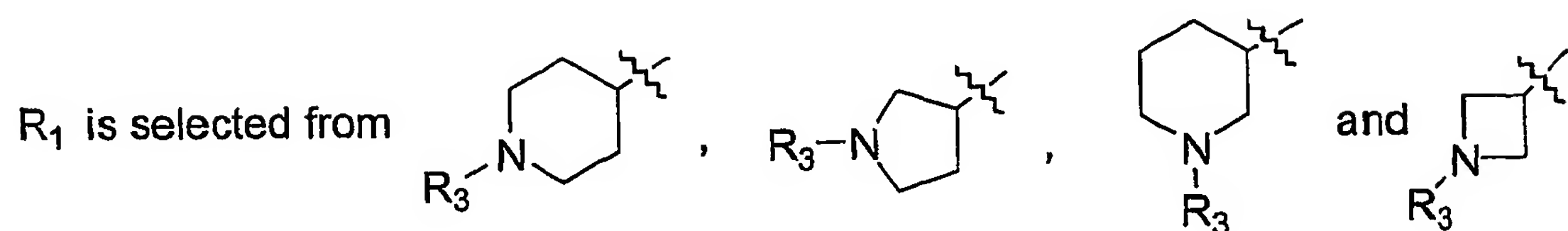
We claim:

1. A compound of Formula I



Formula I

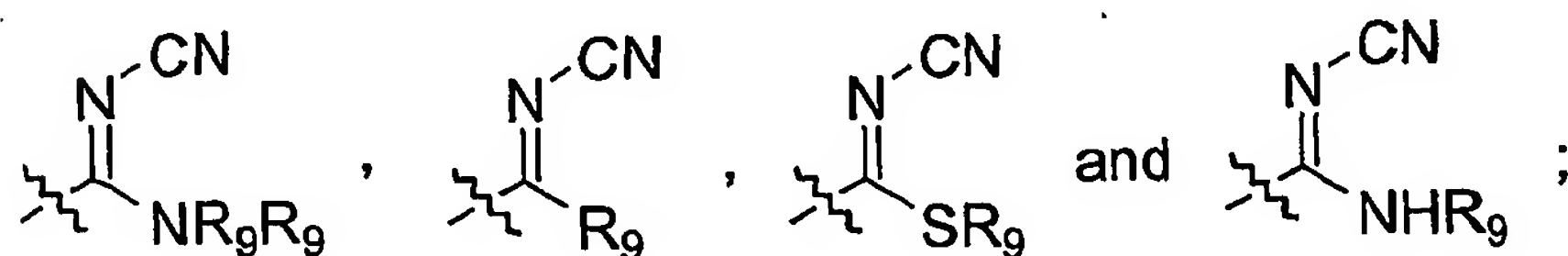
wherein



wherein

- 10 (a) R_3 is selected from H, alkyl, $-\text{COR}_4$, $-(\text{CH}_2)_t\text{heteroaryl}$, $-\text{CHR}_5\text{R}_6$, $-(\text{CH}_2)_t\text{aryl}$, $-\text{SO}_2\text{NR}_5\text{R}_6$, and $-\text{SO}_2\text{R}_9$;
- (b) R_4 is selected from H, $-\text{OR}_5$, alkyl, alkylaryl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, $-(\text{CH}_2)_t\text{OR}_5$, $-(\text{CH}_2)_t\text{NR}_7\text{R}_8$, $-\text{CHR}_5\text{R}_6$, and $-\text{NR}_5\text{R}_6$ optionally forming a cyclic amino derivative;
- 15 (c) R_5 and R_6 are independently selected from H, alkyl, alkylaryl, haloaryl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, and acyl;
- (d) R_7 and R_8 are independently selected from H, alkyl, $-\text{COR}_9$, $-\text{SO}_2\text{R}_9$ and $-\text{CO}_2\text{R}_9$; and
- (e) R_9 is selected from H, alkyl, aryl and alkylaryl;

20 R_2 is selected from $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$,



R_{2a} is H or acyl with the proviso that when R_3 is selected from alkyl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, and $-\text{CHR}_5\text{R}_6$, R_{2a} is H;

25 X is N or CH;

Y is selected from H, halogen, alkoxy, and alkyl; and

t is an integer of 0 to 4;

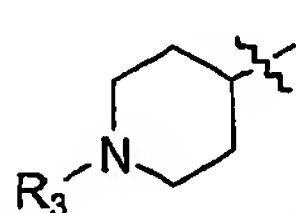
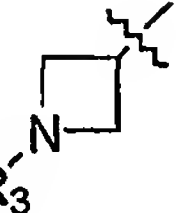
or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture

5 thereof, or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein X is CH.

3. The compound of Claim 1 wherein R_2 is $-C(O)R_9$ wherein R_9 is as claimed in
10 Claim 1.

4. The compound of Claim 3 wherein R_9 is H or alkyl.

5. The compound of Claim 1 wherein R_1 is  or , wherein R_3 is
15 as claimed in Claim 1.

6. The compound of Claim 5 wherein R_{2a} is H and R_3 is selected from $-COR_4$, $-SO_2R_9$ and $-(CH_2)_t$ heteroaryl wherein R_4 , R_9 and t are as claimed in Claim 1.

20 7. The compound of Claim 5 wherein R_4 is selected from $-OR_5$, $-(CH_2)_tOR_5$, alkyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl wherein R_5 and t are as claimed in Claim 1.

8. The compound of Claim 7 wherein R_5 is alkyl and R_9 is H or alkyl.

25 9. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(benzyloxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

30 10. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

11. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(methanesulfonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

5 12. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(methoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

10 13. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(2-pyrimidinyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

15 14. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(3-cyanobenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

15. A compound of Claim 1 of a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(5-cyano-2-pyridyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

20

16. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(2-thienylcarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

25 17. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

30 18. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

19. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

20. A method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said subject a therapeutically effective amount of the compound of Formula I as defined in Claim 1.

21. A method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective amount of the compound of Formula I as defined in Claim 1.

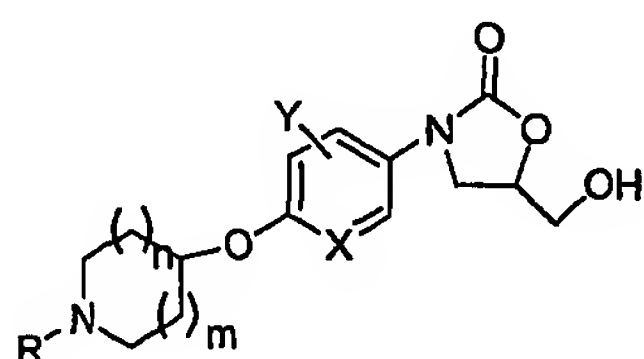
22. The method of Claim 20 or 21 wherein said condition is selected from community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, bone and joint infections, and hospital-acquired lung infections.

23. The method of Claim 20 or 21 wherein said bacterium is selected from *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *Enterococcus spp.*, *Moraxella catarrhalis* and *H. influenzae*.

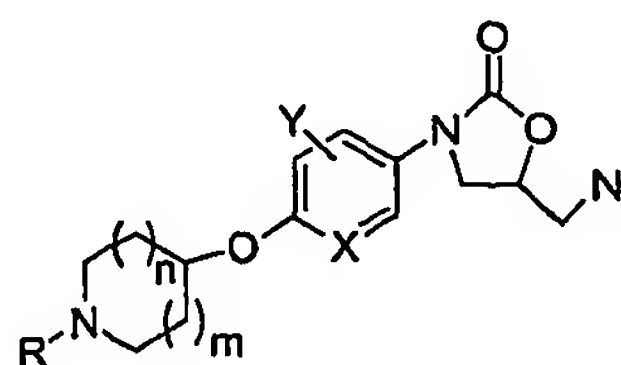
24. The method of Claim 20 or 21 wherein said bacterium is a Gram-positive coccus.

25. The method of Claim 24 wherein said Gram-positive coccus is antibiotic-resistant.

26. An intermediate of Formula e or f



e



f

wherein

R is Boc, $-\text{CH}(\text{Ph})_2$ or $-\text{COCH}_2\text{OCH}_2\text{Ph}$;

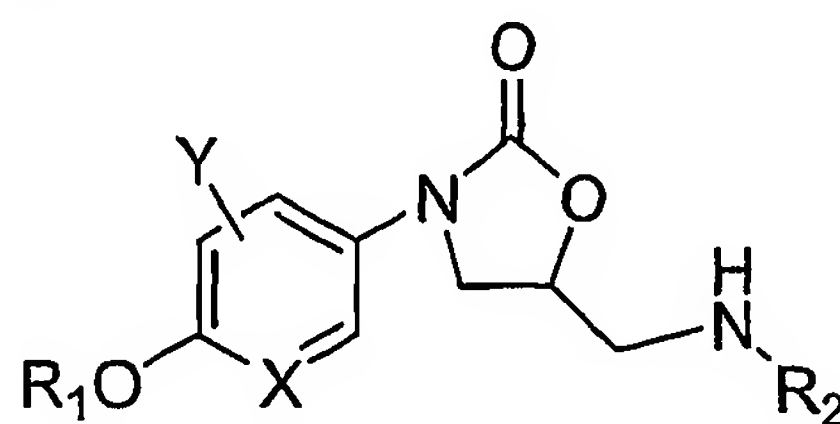
X is N or CH;

5 Y is selected from H, halogen, alkoxy, and alkyl;

n is 0, 1 or 2; and

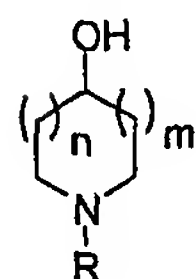
m is 0 or 1.

27. A process for preparing a compound of Formula Ia



Formula Ia

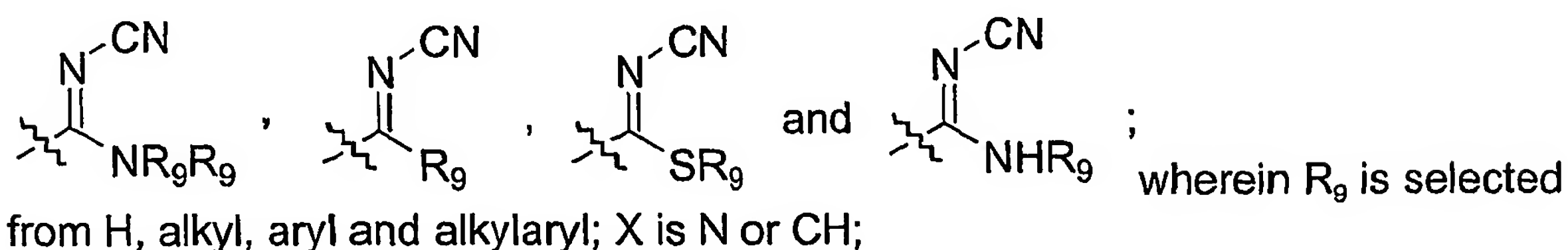
wherein R_1 is a moiety of the formula:



a wherein:

R is selected from Boc, $-\text{CH}(\text{Ph})_2$ or $-\text{COCH}_2\text{OCH}_2\text{Ph}$, n is 0, 1 or 2, m is 0 or 1,

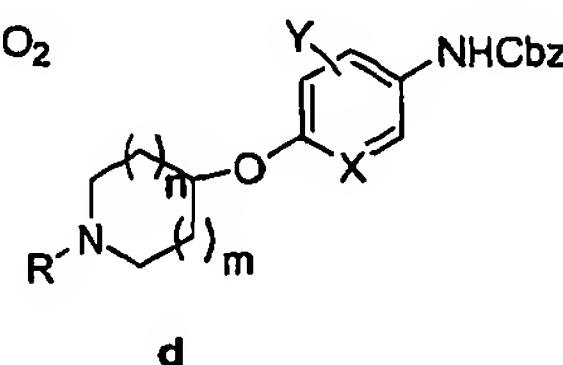
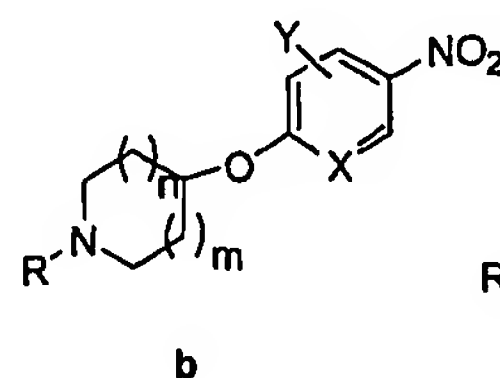
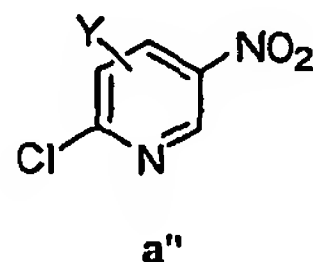
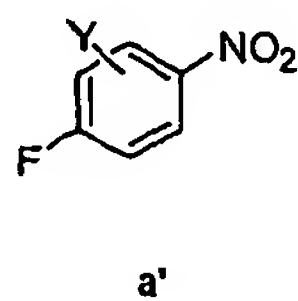
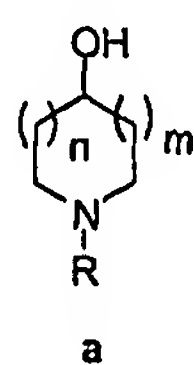
15 R_2 is selected from $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$,



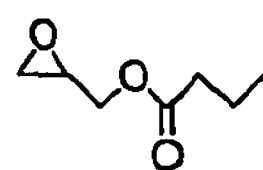
Y is selected from H, halogen, alkoxy, and alkyl;

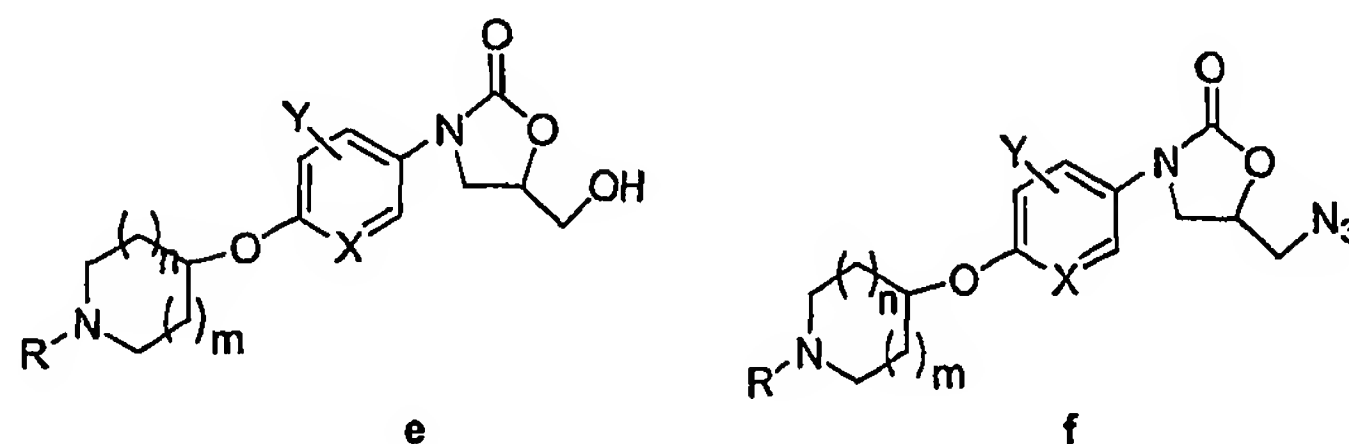
20 which process comprises:

(a) reacting a compound of Formula a with a compound of Formula a' or a'' to form a compound of Formula b;



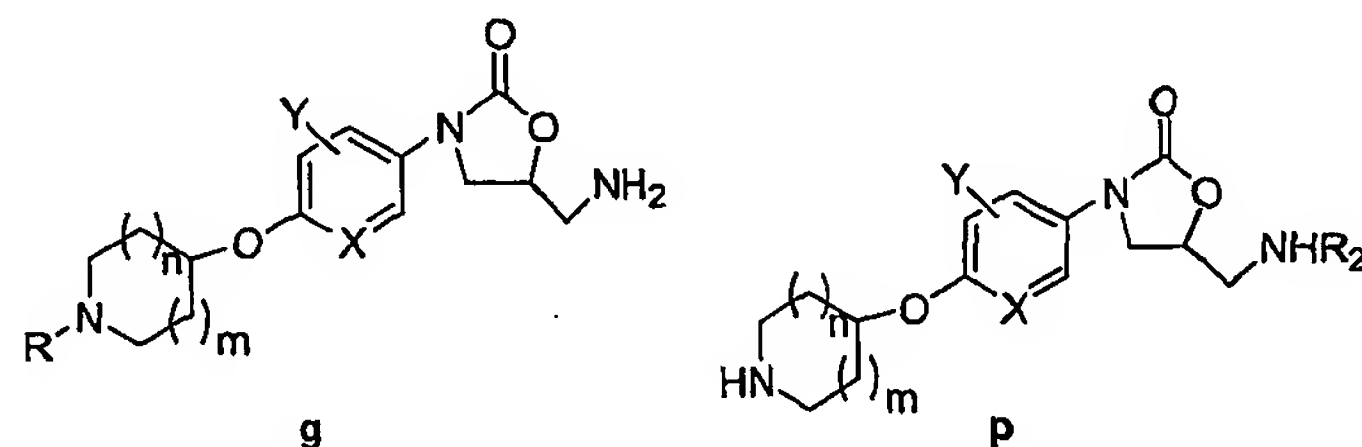
(b) converting the compound of Formula b to a compound of Formula d;

(c) reacting the compound of Formula d with  to form a compound of Formula e;



(d) converting the compound of Formula e to a compound of Formula f;

(e) converting the compound of Formula f to a compound of Formula g;



(f) converting the compound of Formula g to a compound of Formula p; and

(g) converting the compound of Formula p to a compound of Formula la.

INTERNATIONAL SEARCH REPORT

Inter nal Application No

PCT/US 00/33835

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D263/24 C07D413/12 A61K31/42 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 00 27830 A (HOKURIKU SEIYAKU CO., LTD.) 18 May 2000 (2000-05-18) * Examples * claims 1-8	1-27
X	---	26
Y	WO 99 12914 A (HOKURIKU SEIYAKU CO., LTD.) 18 March 1999 (1999-03-18) claims 1-8	1-27
Y	US 4 705 799 A (W. A. GREGORY) 10 November 1987 (1987-11-10) cited in the application claims 1-100	1-27

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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *G* document member of the same patent family

Date of the actual completion of the international search

14 March 2001

Date of mailing of the international search report

20/03/2001

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Authorized officer

Herz, C

INTERNATIONAL SEARCH REPORT

Inter ☐ ☐ Application No
PCT/US 00/33835

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 07271 A (THE UPJOHN COMPANY) 16 March 1995 (1995-03-16) cited in the application claims 1-19 ---	1-27
Y	EP 0 738 726 A (BAYER AG) 23 October 1996 (1996-10-23) claims 1-7 ---	1-27
Y	EP 0 127 902 A (E.I. DU PONT DE NEMOURS AND COMPANY) 12 December 1984 (1984-12-12) claims 1-11 -----	1-27

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Information on patent family members

International Application No

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Information on patent family members

Internal Application No

PCT/US 00/33835

Form PCT/SA/210 (patent family annex) (July 1992)

Information on patent family members

PCT/US 00/33835

Form PCT/ISA/210 (patent family annex) (July 1982)